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**Copper Mediated Atom Transfer Radical**  
**Cyclisation Reactions**

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**For the Degree of Ph.D.**

**The University of Warwick Department of Chemistry**

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*To Mum, for making this possible.*

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/



## **Declaration**

The work described within this thesis is the original work of the author unless were stated, and was conducted between October 1998 and September 2000 at the University of Warwick.

## **Abstract**

The effect of different *N*-pentyl-2-pyridylmethanimine (NPMI) derivatives upon the rate of copper(I) mediated atom transfer radical cyclisation (ATRC) of mono-bromo- and trichloro-acetamides were investigated. 6-Functionalised NPMI derivatives retarded the rate of ATRC due to steric effects, while for the 5-substituted analogues, inductively increasing the electron density of the pyridine nitrogen increased the rate of ATRC. Multidentate amine derived copper(I) halide complexes were found to mediate the ATRC of 1-halo-*N*-propargylacetamides. The cyclisation of trichloro- and dichloroacetamide precursors leads to  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams containing the gem-dihalide functional group, while monohaloacetamides gave rise to either cyclised atom transfer or reduction products depending upon the solvent and catalyst used. The tripyridylamine (TPA) copper(I) halide complex facilitates the efficient ATRC of bromo-enamides to give  $\beta$ -lactams exclusively with no formation of  $\gamma$ -lactams. Initial products result from 4-*exo* bromine atom transfer and subsequent elimination can be readily achieved to furnish the corresponding alkenes. A range of fused bicyclic lactams were prepared *via* copper(I) mediated 5-*endo* ATRC of halo-*N*-(cycloalk-1-enyl)acetamides and the use of this methodology for the synthesis of the lycorane and erythrinane alkaloid skeletons was investigated.

## Abbreviations

AIBN	Azobisisobutyronitrile
ATRC	Atom transfer radical cyclisation
ATRP	Atom transfer radical polymerisation
Bipy	2,2'-Bipyridine
Bn	Benzyl
DBU	1,8-Diazobicyclo[5.4.0]undecene-7
DCE	Dichloroethane
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ESR	Electron spin resonance
Et	Ethyl
HOMO	Highest occupied molecular orbital
Hz	Hertz
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
Me <sub>6</sub> -tren	<i>N,N,N',N',N'',N''</i> -Hexamethyltriethylenetetramine
MMA	Methyl methacrylate
NMR	Nuclear magnetic resonance
n.O.e	Nuclear Overhauser effect

NPMI	<i>N</i> -Pentyl-2-pyridylmethanimine
PCC	Pyridinium chlorochromate
PDI	Polydispersities
PMB	<i>para</i> -Methoxy benzyl
SOMO	Singly occupied molecular orbital
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TPA	Tris-(2-pyridyl-methyl)-amine
TTMSS	Tris(trimethylsilyl)silane
UV	Ultra violet

## **Chapter 1**

### **Introduction**

#### **1.1 General introduction.**

Free radicals are species containing one or more unpaired electrons. This definition includes certain stable inorganic molecules such as NO and NO<sub>2</sub>, and many monatomic species, such as Na and Cl. In contrast to ionic species, radicals react together without encountering any significant barrier to form stable neutral molecules. Hence, in the liquid phase radical-radical reactions are often limited only by the rate at which the reaction partners can diffuse through solution.<sup>1</sup> However, persistent radicals have appreciable lifetimes due to steric factors and can allow the rates of such reactions to be slowed.

This reactive nature, coupled with significant undesirable solvent side reactions limits the synthetic utility of radical-radical reactions. However, reactions of radicals and non-radicals can be conducted in a more controlled manner and this has much more scope for synthetic development.

Radicals are synthetic intermediates of considerable importance, and when compared to their ionic counterparts have a number of unique features. Radical reactions typically proceed with significant functional group tolerance and with high levels of regio- and stereoselectivity. Radical reactions are often tolerant of steric crowding, particularly at

the radical centre and the application of heat can often be avoided by utilising photolysis for radical generation. In addition, radicals are free from solvent, counterion and aggregation effects.

## 1.2 Carbon radicals.

As the employment of free radicals in organic synthesis continues to grow in popularity much effort has focussed on the use of carbon centred radicals. The work in this thesis covers the generation and reaction of carbon centred radicals and as such an introduction to their chemistry only is given here.

### 1.2.1 Stability and structure.

Dissociation energies ( $D$  values) of R-H bonds provide a measure of the relative inherent stability of free radicals. Table 1 lists these energies for selected carbon centred radicals (R),<sup>2</sup> the higher the  $D$  value, the less stable the radical.

R	$D$ ( kJ / mol )	R	$D$ ( kJ / mol )
Ph <sup>•</sup>	464	Pr <sup>•</sup>	417
CF <sub>3</sub> <sup>•</sup>	446	Cl <sub>3</sub> C <sup>•</sup>	401
CH <sub>2</sub> =CH <sup>•</sup>	444	Me <sub>2</sub> CH <sup>•</sup>	401
Cyclopropyl <sup>•</sup>	444	Cyclohexyl	400
Me <sup>•</sup>	438	PhCH <sub>2</sub> <sup>•</sup>	368
Et <sup>•</sup>	419	CH <sub>2</sub> =CHCH <sub>2</sub> <sup>•</sup>	361
Me <sub>3</sub> CCH <sub>2</sub> <sup>•</sup>	418		

Table 1. Selected bond dissociation energies.

Note that the order of stability of free radicals is tertiary > secondary > primary > methane. This series is analogous to that in carbocations and is explainable by hyperconjugation. The stability of free radicals also increases with resonance possibilities.<sup>3</sup> Thus, allylic and benzylic radicals, for which conical forms can be drawn are substantially more stable than simple alkyl radicals.

Carbon centred radicals may either adopt a planar ( $sp^2$  bonding) or pyramidal ( $sp^3$  bonding) structure as outlined in figure 1. ESR spectra, and other evidence, indicate that simple alkyl radicals have planar structures.<sup>4</sup> This is in accordance with the observed loss of optical activity when a radical is generated at a chiral carbon.<sup>5</sup> Although simple alkyl radicals prefer a planar geometry the energy difference between planar and pyramidal radicals is relatively small. However, radicals with electron withdrawing substituents (e.g.  $CF_3^\bullet$ ) prefer a pyramidal structure,<sup>6</sup> hence, increasing electronegativity favours deviation from planarity.



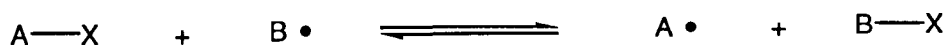
**Figure 1. Structure of alkyl radicals.**

### 1.3 Radical reactions.

The increase in synthetic application and development of radical reactions may partly be attributed to the large number of kinetic and mechanistic studies that have been conducted.<sup>7</sup> The large variety of useful transformations that can now be accomplished using free radical reactions has been extensively covered in a number of reviews.<sup>8</sup> Most of these reactions can be classified into two broad groups: atom (or group) transfer and addition to multiple bonds.

### 1.4 Atom transfer reactions.

In atom transfer reactions,<sup>9</sup> a radical directly attacks and displaces an atom or group from an organic molecule to produce a new radical located at the former site of the abstracted functionality (scheme 1). These direct substitutions are analogous to the S<sub>N</sub>2 or S<sub>E</sub>2 displacements of heterolytic chemistry and are termed S<sub>H</sub>2 substitution reactions (also called abstractions).



**Scheme 1. Atom transfer reaction.**

In this very broad class of reaction the most commonly abstracted groups are univalent atoms such as hydrogen or halogens, although abstraction of other groups (e.g. SR) are



also useful. The position of equilibrium is determined by the relative strengths of the forming and breaking bonds. Hence, the rate of reaction is controlled largely by its exothermicity.

### 1.5 Addition reactions.

The addition of radicals to multiple bonds is an important class of reaction and is one of the mildest techniques available to extend a carbon chain. Although additions to alkenes and alkynes has received most attention,<sup>8,10</sup> additions to carbon-nitrogen and carbon-oxygen bonds have begun to emerge as useful reactions. Both inter- and intramolecular radical additions are common. However, intramolecular addition is pertinent to the work described within this thesis and will be covered in more detail.

#### 1.5.1 Intermolecular addition.

Carbon-carbon bond formation is arguably the most important synthetic step in the construction of organic molecules and is increasingly being achieved by the addition of carbon centred radicals to carbon-carbon multiple bonds (scheme 2.).

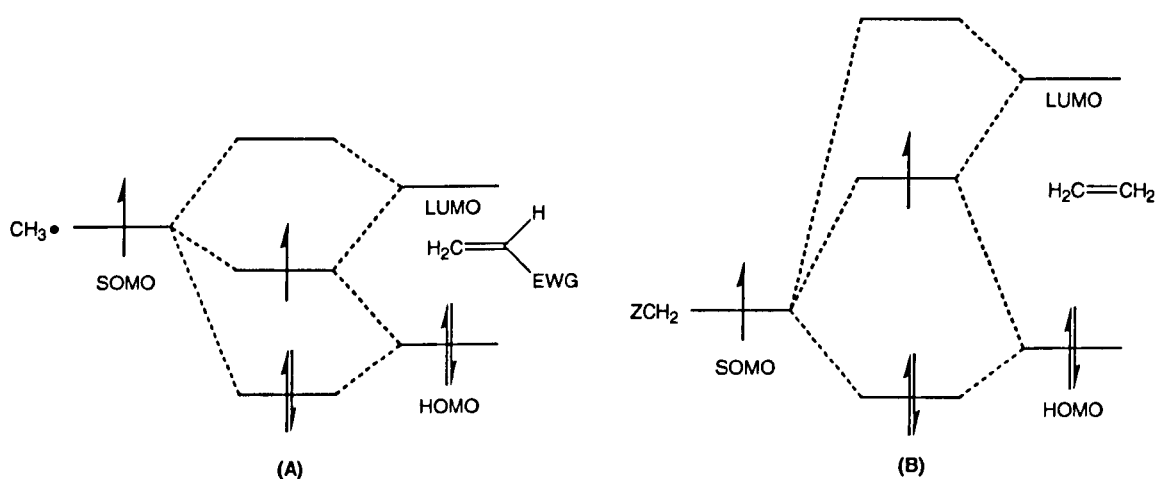


**Scheme 2. Radical addition reaction.**

This addition is often a highly energetically favourable process since a C-C  $\sigma$ -bond is formed at the expense of a C-C  $\pi$ -bond. The effects of substituents located on both the radical and the unsaturated partner on the rate and regioselectivity of the reaction are well established.<sup>11</sup>

### 1.5.1.1 Electronic character of carbon radicals.

Carbon centred radicals can be classified as nucleophilic, electrophilic or ambiphilic depending upon the substituents attached to the radical. This electronic nature will determine the radicals reactivity. The origin of these substituent effects in radical additions to alkenes can be understood in terms of frontier molecular orbitals. The important interactions occur between the radicals singly occupied molecular orbital (SOMO) and the alkenes highest occupied orbital (HOMO) and lowest unoccupied orbital (LUMO) as represented in figure 2.<sup>7</sup>



**Figure 2. Frontier orbital diagram for radical addition to an alkene.**

Nucleophilic radicals including vinyl, aryl, acyl and alkyl radicals react preferentially with electron deficient alkenes. Intermolecular additions to unactivated alkenes are generally too slow to be synthetically useful. However, reaction rates can be increased by electronic modification of the alkene partner. Thus, intermolecular additions can be greatly accelerated by introducing an electron withdrawing substituent at the  $\beta$ -position of the alkene.<sup>9</sup> This serves to lower the LUMO thereby decreasing the SOMO-LUMO gap resulting in stabilisation of the transition state (figure 2, diagram A).

Electrophilic radicals generally contain two electron withdrawing groups and react preferentially with electron rich alkenes. The introduction of electron withdrawing substituents at the radical centre will have the effect of lowering the SOMO, which permits stronger SOMO-HOMO interactions resulting in an increase in reaction rate (figure 2, diagram B). Electron donating substituents on the alkene have a similar effect but to a much lesser extent.<sup>12</sup>

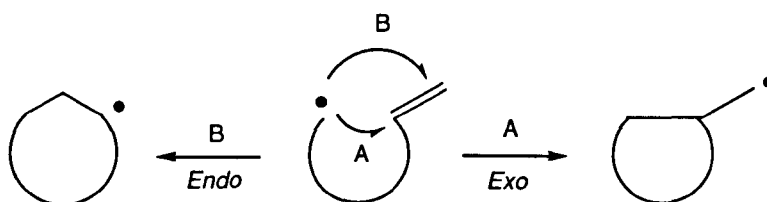
Distinction between electrophilic and ambiphilic radicals is unclear. Generally ambiphilic radicals possess SOMO energies between those of electrophilic and nucleophilic radicals.

### 1.5.2 Intramolecular addition (cyclisation).

The preparation of cyclic systems is fundamental to the synthesis of complex natural products. However, it was not until the early 1980's that Stork,<sup>13</sup> Bachi<sup>14</sup> and Beckwith<sup>15</sup> among others started to explore the synthetic utility of intramolecular free radical additions. Radical cyclisation reactions have gained increasing attention and now represent an extremely powerful tool for the construction of cyclic arrays.

This section outlines the scope of such methodologies. Work described within this thesis mainly concerns *exo* cyclisations and as such emphasis will be placed upon this area.

In every radical cyclisation to an alkene there are two competing pathways: An *endo* cyclisation involves a radical addition to the terminal end of the multiple bond resulting in a larger ring, while an *exo* cyclisation occurs when the radical attacks the internal end forming a smaller ring (scheme 3).



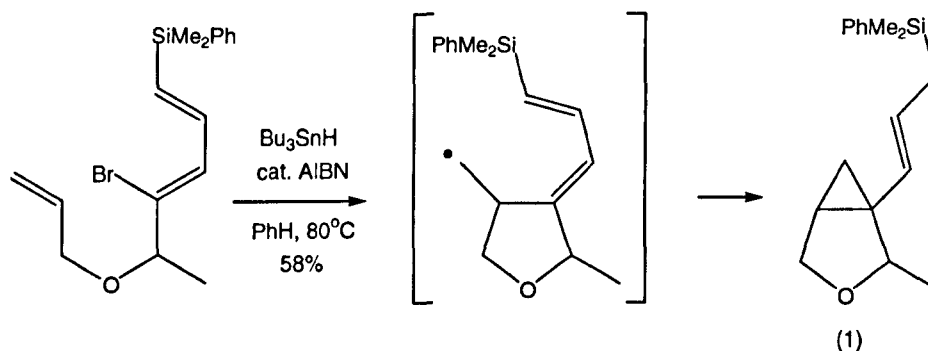
**Scheme 3. *Exo/endo* pathway of intramolecular radical additions.**

#### 1.5.2.1 *Exo* cyclisations.

Intramolecular radical additions are generally regioselective and in accordance to Baldwin's rules<sup>16</sup> favor 3 to 7-*exo* cyclisations over their *endo* counterparts. In addition, activating suitable radical acceptors with an electron withdrawing group at the terminus of the carbon-carbon multiple bond will improve both regioselectivity and yield.

### 1.5.2.1.1 3- and 4-Membered ring formation.

Radical cyclisations to form three- and four-membered rings do not compete well with the reverse ring opening process and are therefore highly unfavourable. The release of ring strain strongly biases the equilibrium toward the direction of the acyclic radicals. However, radical cyclisations that form three-membered rings have been observed if the ring closed radical is resonance stabilised, for example, Luh and Weng have demonstrated sequential 5-*exo* and 3-*exo* cyclisations leading to the formation of fused cyclopropanes (**1**)<sup>17</sup> (scheme 4).



**Scheme 4. Formation of fused cyclopropanes (1).**

A few literature examples have demonstrated that suitably designed radical acceptors can accelerate 4-*exo* cyclisations and stabilise the resulting ring closed radicals.<sup>18</sup>  $\beta$ -Lactams have been synthesised by several different methods using radical cyclisation protocols.<sup>19</sup> All these methods have some mechanistic factor that promotes the otherwise

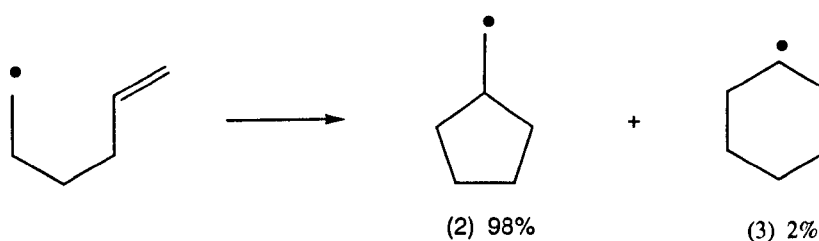
unfavourable 4-membered ring formation. This area will be discussed in more detail in chapter 4.

### 1.5.2.1.2 Hexenyl radical cyclisations.

The formation of five-membered rings by *5-exo* cyclisation of hexenyl radicals are the most useful class of radical cyclisation reaction. These cyclisations are typically irreversible and have been studied kinetically and mechanistically in some detail.<sup>20</sup>

#### 1.5.2.1.2a Regioselectivity.

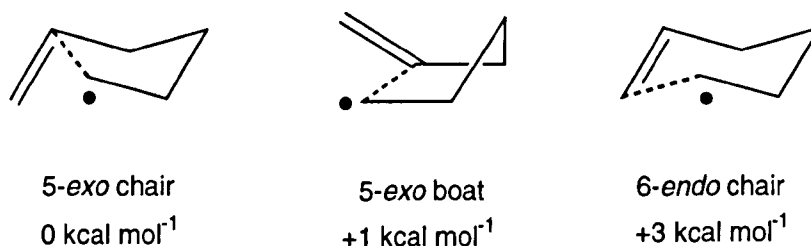
5-Hexenyl radical cyclisation results in the formation of both the *5-exo* derived methylcyclopentyl radical (**2**) and the *6-endo* derived cyclohexyl radical (**3**) in a ratio of 49:1 (scheme 5).<sup>11</sup>



**Scheme 5. regioselectivity of 5-hexenyl radical cyclisation.**

On thermochemical grounds the more stable cyclohexyl radical (**3**) would be expected to give cyclohexane as the major product. However, cyclisation proceeds predominantly *via* 5-*exo* ring closure demonstrating the reaction to be under kinetic control.<sup>21</sup>

The transition state model devised by Beckwith<sup>22</sup> predicts that the main product of cyclisation occurs *via* the lowest energy strain-free 5-*exo* chair transition state (figure 3). It is suggested that this arrangement accommodates maximum overlap between the semi occupied 2p orbital and the vacant  $\pi^*$  orbital.<sup>23</sup> This stereoelectronic influence is regarded as the single most important factor favoring 5-*exo* over 6-*endo* cyclisations.<sup>24</sup>

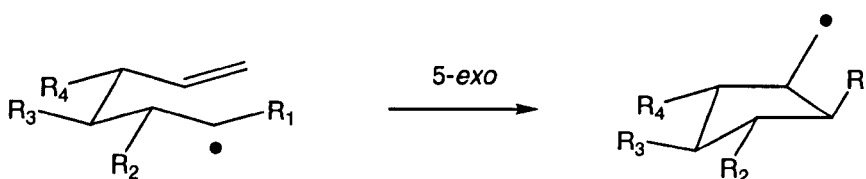


**Figure 3. Transition state models for 5-hexenyl radical cyclisation.**

#### 1.5.2.1.2b Stereoselectivity.

The stereochemical outcome of the cyclisation of substituted 5-hexenyl radicals has been well studied. The Beckwith-Houk chair-like transition state model serves as the basis for predicting and rationalising the stereoselectivity of such reactions.<sup>22b, 25</sup> Later work by Spellmeyer and Houk<sup>25</sup> advanced this understanding and recognised the importance of the 5-*exo* boat transition state. The model states that major cyclisation products are

formed *via* a chair-like transition state with substituents preferentially occupying *pseudo-equatorial* positions as depicted in scheme 6.



**Scheme 6. Beckwith model for stereoselectivity of 5-hexenyl radical cyclisations.**

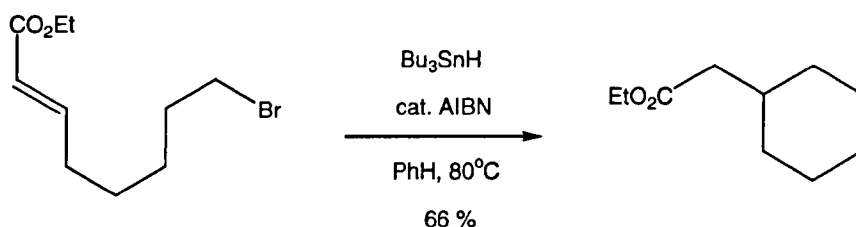
Thus, the model predicts *cis* products from 1- or 3-substituted hexenyl radicals and predominantly *trans* products from 2- or 4-substituted radicals. The energy difference between two conformers of a cyclic transition state corresponds to the conformational preference of the substituents. Therefore, stereoselectivity is most pronounced when substituents are sterically bulky.

#### 1.5.2.1.3 Formation of larger rings.

The formation of six-membered rings by *exo* cyclisation of 6-heptenyl radicals is significantly slower than that of their 5-hexenyl counterparts. The *exo* mode of ring closure is still favoured, however competition between 6-*exo* and 7-*endo* cyclisation is of greater importance since the increased chain length now permits the formation of greater amounts of the *endo* derived product. In addition, heptenyl radical cyclisations are complicated further by a competing 1,5-hydrogen atom transfer reaction. As with ring



closure of other sizes, electron-withdrawing substituents at the terminus of the multiple bond have been employed to accelerate 6-*exo* cyclisation (scheme 7).<sup>26</sup>



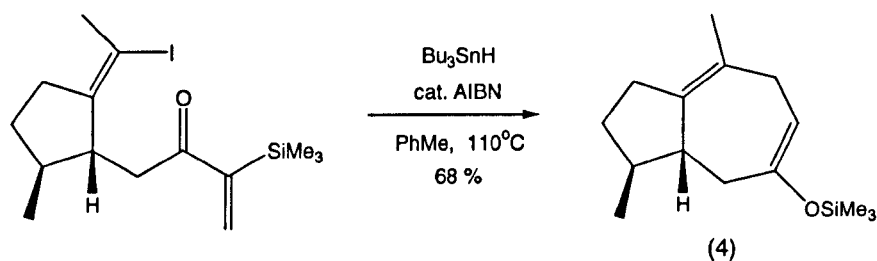
**Scheme 7. Example of 6-*exo* ring closure.**

Stereoselectivities of 6-*exo* cyclisations of substituted heptenyl radicals are still predictable using the transition state model, but with some limitations.<sup>27</sup> The model predicts formation of *cis* products from 2- and 4-substituted radicals, and *trans* from 1-, 3- and 5-substituted radicals. Hanessian<sup>26</sup> systematically studied 6-*exo* closures of substituted heptenyl radicals and other examples of stereoselective 6-*exo* cyclisations appear in the literature.<sup>28</sup>

The Porter and Hutchinson groups<sup>29</sup> have demonstrated that formation of larger rings *via* *exo*-cyclisations can be achieved. However, in general terms, as the size of the ring increases the rate of closure decreases as does the preference for *exo* mode of cyclisation.

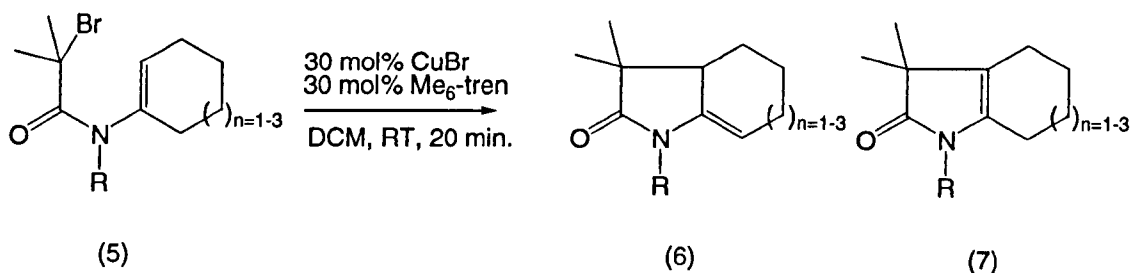
### 1.5.2.2 *Endo* cyclisations.

In comparison to their *exo* counterparts, *endo* cyclisations are usually minor processes in the formation of standard and medium sized rings. However, appropriately designed radical acceptors have the ability to change the regioselectivity to favor *endo* cyclisation. For example, *endo* cyclisations for larger ring closures are favourable when an electron withdrawing group is present at the inner position of the multiple bond. This concept is exemplified by the synthesis of 7-*epi*- $\beta$ -bulnesene (**4**) by Negishi and coworkers (scheme 8).<sup>30</sup>



**Scheme 8. Synthesis of 7-*epi*- $\beta$ -bulnesene via *endo* cyclisation.**

In addition, suitably designed halo-enamide substrates have been reported, within the Clark group, to undergo 5-*endo* cyclisation.<sup>31</sup> Thus, reaction of mono-halo substrates (**5**) ( $n=1$ ,  $R=\text{Bn}$ ) furnished two alkene products (**6**) and (**7**) in 82% yield (1:1 ratio) (scheme 9). The reaction was found to be tolerant of a variety of ring sizes and ring substitutions. This area will be covered in more detail in chapter 4.



**Scheme 9. 5-Endo cyclisation of monohalo enamides (5).**

In contrast to smaller ring formation, most radical macrocyclisations that appear in the literature are designed to utilise *endo* ring closures. Porter and co-workers pioneered the synthesis of macrocyclic ketones and lactones by radical cyclisation reactions.<sup>32</sup> Boger and Pattenden among others extended this chemistry to include acyl and allyl radical cyclisations and applied this methodology to the synthesis of a series of biologically interesting compounds.<sup>33</sup>

The construction of complex heterocyclic systems is increasingly achieved *via* radical cyclisation protocols. *Endo* cyclisations are often employed for this purpose, particularly in the preparation of fused ring systems. The formation of such systems using the less common 5-*endo* mode of cyclisation will be discussed in detail in chapter 5.

## 1.6 Methods of performing radical reactions.

A diverse range of transformations can be achieved using free radical reactions. However, the number of practical methods available to conduct free radical reactions is quite limited. The work reported in this thesis utilises copper mediated atom transfer reactions for the generation of radicals, and hence this section will be discussed at length. For synthetic application the selection of method is extremely important as it will determine the fate of intermediate radicals. Identical radicals generated by different methods may have different lifetimes and therefore provide different products.<sup>27</sup>

## 1.7 Chain reactions.

The maintenance of a low concentration of radicals over the course of a reaction is desirable since unlike anions and cations, radicals react with themselves at rates approaching the diffusion controlled limit. Chain reactions are well suited to meet this requirement. Chain reactions consist of initiation, propagation and termination steps. Initiation steps generate radicals and are often achieved by homolytic bond cleavage of an initiator (AIBN, BPO) or by a photochemical or redox reaction. All desired transformations in a chain occur in the propagation steps, while termination steps remove radicals *via* dimerisation and disproportionation reactions.

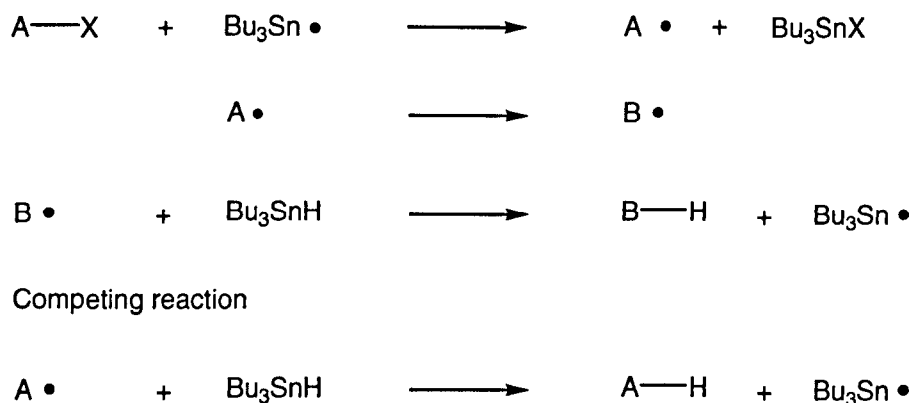
To be useful synthetically, a given chain reaction must generate radicals selectively and these radicals must have sufficient lifetime to react. This lifetime must be carefully

controlled by the nature of the chain transfer step since radicals that are permitted too long a lifetime may engage in chain termination steps.

## **1.8 Metal Hydrides.**

### **1.8.1 The tin hydride method.**

The use of organotin hydrides has become the most commonly used method for the synthetic application of free radicals to carbon-carbon bond formation.<sup>34</sup> The characteristics of this approach are outlined below in a generalised example of a tributyltin hydride ( $\text{Bu}_3\text{SnH}$ ) mediated reaction (scheme 10). Typically the chain carrier  $\text{Bu}_3\text{Sn}^\bullet$ , is generated in an initiation step from tributyltin hydride using azobisisobutyronitrile (AIBN) as a chemical initiator. The tributyltin hydride radical then abstracts an atom or group X from the precursor to generate the organic radical  $\text{A}^\bullet$ . This then undergoes a transformation (inter- or intramolecular) to form a new radical  $\text{B}^\bullet$ . Hydrogen atom transfer then provides the final product B-H and regenerates the chain carrying tributyl tin radical.



**Scheme 10. Tributyltin hydride mediated radical reactions.**

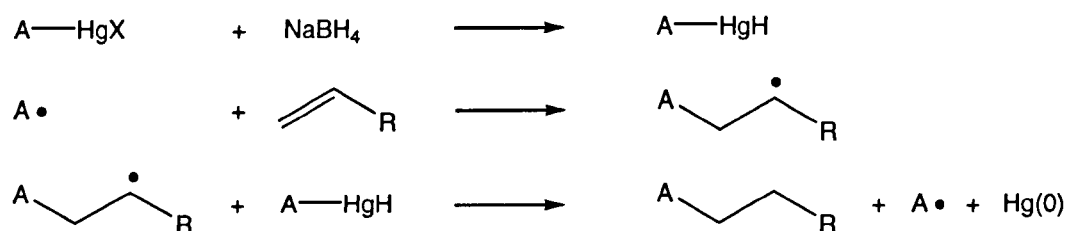
A common problem in organostannane mediated reactions is the premature reduction of  $\text{A}^\bullet$  by the reagent itself. The maintenance of a low concentration of the hydride reagent over the course of the reaction is therefore desirable. Hence, syringe pump techniques are often used for the addition of the hydride and serve to maintain a steady, low concentration of this reagent. Related techniques include the use of polymer bound tin hydrides<sup>35</sup> and the generation of trialkyltin hydrides *in-situ* by the reaction of a catalytic amount of tin halide with standard hydride reducing agents ( $\text{NaBH}_4$  or  $\text{NaCNBH}_3$ ).<sup>36</sup>

A variety of radical precursors can be used in the tin hydride method. A reactivity scale has been determined by Beckwith and Pigou.<sup>37</sup> They established in order of decreasing reactivity that  $\text{I} > \text{Br} > \text{PhSe} > \text{secondary and tertiary xanthate esters} > \text{tertiary nitro} > \text{Cl} > \text{PhS} > \text{MeS}$ . For the least reactive alkyl chlorides and alkyl phenyl sulfides the rate of abstraction may not be sufficient to propagate a chain. In general, iodides are the precursor of choice since trialkyltin radicals abstract iodine from alkyl iodides at rates approaching the diffusion controlled limit.

Despite this versatility, there are major disadvantages associated with the use of trialkyltin hydride mediated radical reactions. These include their high toxicity, high expense, their reductive nature and the difficulty in removing tin compounds from product mixtures.

### 1.8.2 Mercuric Hydrides.

The use of mercuric hydrides to conduct radical chain reactions has been developed by Giese.<sup>38</sup> The mercuric hydride reagent is generated *in-situ* by the reduction of alkyl mercuric salts (typically halides or acetates) with hydride donors such as NaBH<sub>4</sub>. Thermal or photochemical initiation is unnecessary in this method as the chain is started by spontaneous decomposition of the mercuric hydride. This approach has several advantages over the tin method as reactions proceed under mild conditions, are rapid and the separation of mercury during work-up is non-problematic.<sup>27</sup> However, reduction is facile due to superior hydrogen transfer from mercuric hydrides. Thus, this methodology is typically only employed in syntheses involving reactive, electron-poor alkenes as summarised in scheme 11.<sup>39</sup>

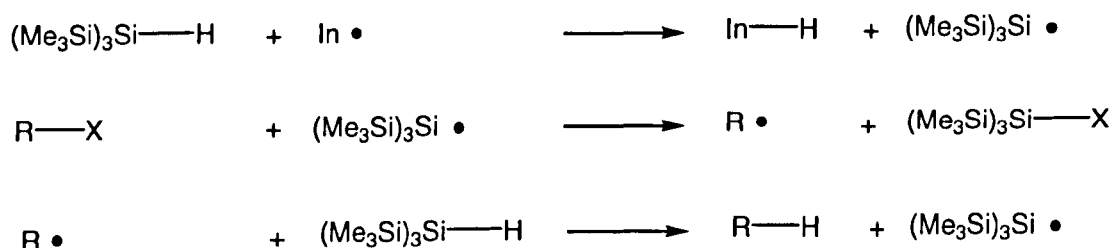


Scheme 11. Chain reaction for mercuric hydride.

### 1.8.3 Tris(trimethylsilyl)silane method.

Tris(trimethylsilyl)silane (TTMSS) has been reported to be an efficient free radical mediator due to a relatively weak Si-H bond which enables it to participate in radical chain reactions as a hydrogen donor.<sup>40</sup> TTMSS is an effective radical mediator with alkyl bromides and iodides, isocyanides, selenides and carbonyl derivatives.<sup>41</sup>

The non-toxic TTMSS is environmentally superior to trialkyl tin hydrides and the ease of purification of products makes it an attractive reagent. The use of TTMSS has a further advantage over trialkyl tin hydrides as TTMSS is a poorer hydrogen donor, therefore lower rates of hydrogen transfer are achieved leading to the formation of less reduction product. The mode of action of TTMSS is analogous to that of tin hydride as shown in scheme 12.



**Scheme 12. Chain reaction using Tris(trimethylsilyl)silane.**



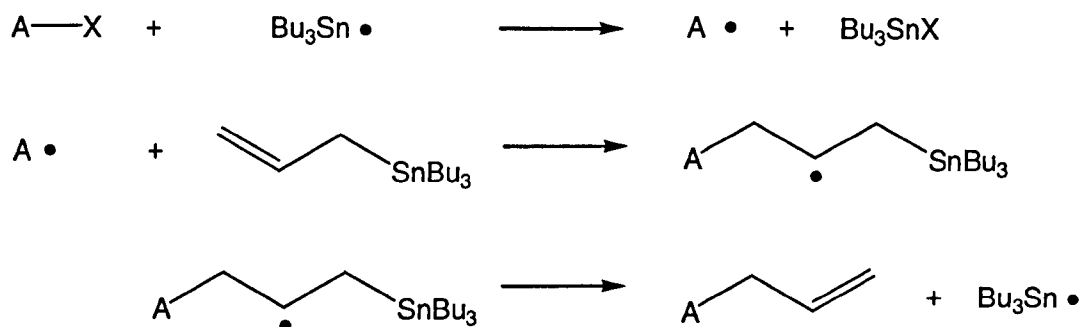
## 1.9 The fragmentation method.

The fragmentation method involves the generation of the chain-transfer agent by a fragmentation reaction (scheme 13) rather than by an atom abstraction as in the tin hydride method.



**Scheme 13. Generation of the chain transfer agent.**

The rapid fragmentation of an appropriate C-Y bond produces the radical  $\text{Y}^\bullet$ , which may be the chain-transfer agent itself or generate the chain-transfer reagent in a subsequent reaction with a neutral molecule. Instead of obtaining reduced products, substitution products are formed as an alkene is regenerated in the fragmentation step. The process utilises the fact that relatively weak bonds such as C-Br, C-SnR and C-SR can fragment if located  $\beta$  to a radical. Allyl and vinyl stannanes have become the most popular reagents for this method. The chain mechanism for allylation with allyltributylstannane is shown in scheme 14. Abstraction of X (normally a halogen) by the tributyltin radical provides a carbon radical from the organic substrate. Addition of the generated radical  $\text{A}^\bullet$  to allyltributylstannane, followed by  $\beta$ -scission then affords the allylated product and regenerates the tributyl tin radical in order to propagate the chain.

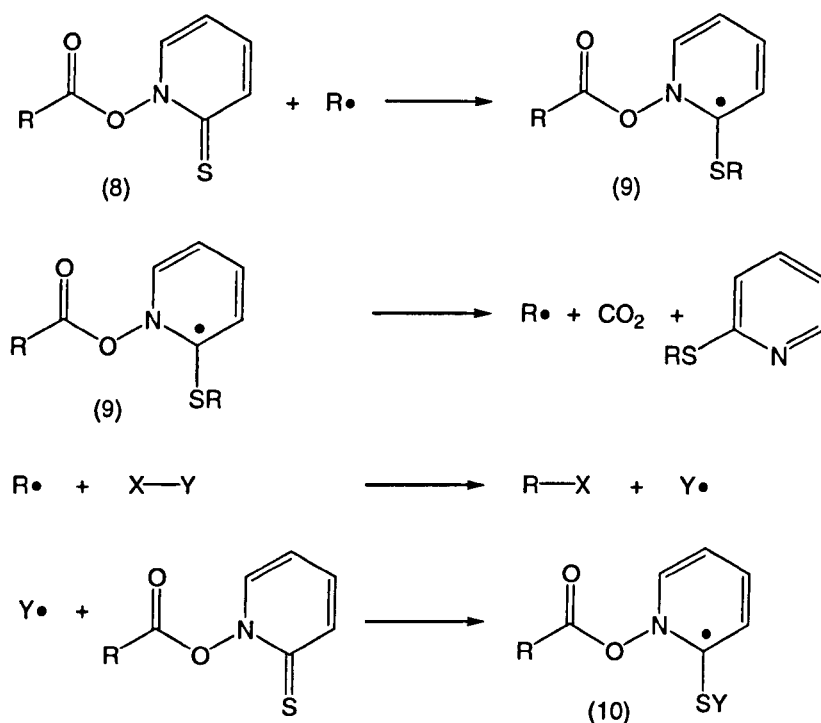


**Scheme 14. Chain reaction for allyltributylstannane mediated allylation.**

The advantage of this approach is that tin hydride is not required in the reaction. Hence, the lifetimes of intermediate radicals are not limited by the rate of hydrogen atom abstraction and since intermediate radicals are not intercepted low concentrations are not required. This ability to provide long lifetimes for intermediate radicals is the key element in the success of the fragmentation method and often allow one or more reactions to be conducted between radical generation and allylation.<sup>42</sup>

### 1.10 The thiohydroxamate ester method.

This method was developed by Barton and co-workers<sup>43</sup> and utilises the chemistry of thiohydroxamate acid esters. The thiohydroxamate ester approach differs from other methods in that group transfer is achieved by an addition/elimination mechanism rather than by a homolytic substitution. Mechanistic studies by Barton have provided good evidence for the propagation sequence as outlined in scheme 15.<sup>44</sup>



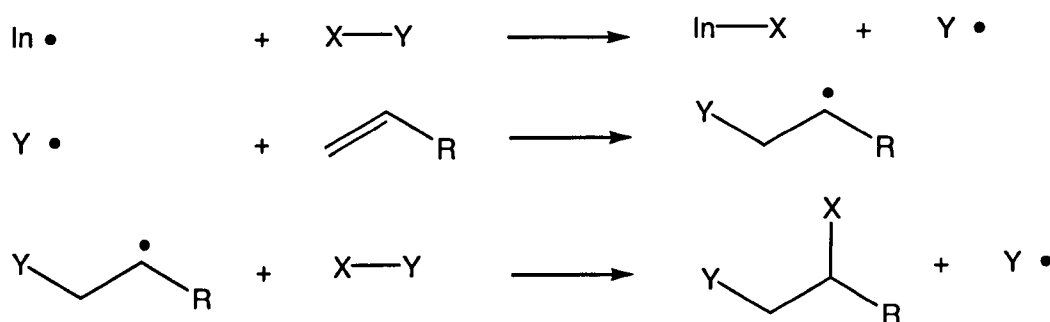
**Scheme 15. Propagation sequence for thiohydroxamate ester method.**

Initial addition of the alkyl radical  $\text{R}\cdot$  to the thiohydroxamate (8) produces (9). Fragmentation of (9) then occurs and may be concerted or stepwise, involving an intermediate carboxy radical. The alkyl radical  $\text{R}\cdot$  is the chain carrying species. The formation of carbon dioxide and the aromatization to the mercaptopyridine provide the enthalpic driving force for the reaction. For the successful formation of products  $\text{R-X}$  the alkyl radical must abstract an atom or group (X) from  $\text{X-Y}$  at a rate more rapid than the direct addition to the starting hydroxamate. The resulting radical  $\text{Y}\cdot$  then adds to the precursor to produce (10), which itself fragments to transfer the chain.

The power of the Barton method lies in the ability of the intermediate radical  $R^\bullet$  to be intercepted by a variety of other neutral molecules,  $X-Y$ . A wide range of functional groups  $X$  can thus be incorporated using this general approach.

### 1.11 The atom transfer method.

Developed by Kharasch, the addition of a reagent  $X-Y$  across a carbon-carbon multiple bond is one of the fundamental reactions of organic free radicals.<sup>45</sup> A general mechanism for this addition (or cyclisation) reaction is outlined in scheme 16.



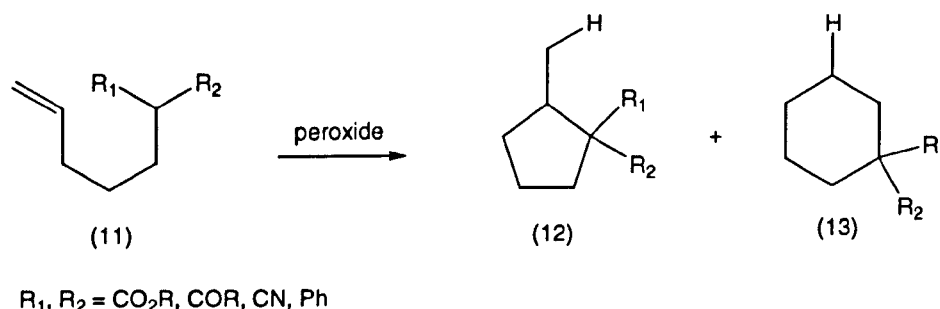
**Scheme 16. Atom transfer reaction scheme.**

The key chain transfer step involves donation of an atom or group  $X$  from the starting material  $X-Y$ , with the resulting radical  $Y^\bullet$  being the chain transfer agent. Therefore, in effect, both chain transfer and generation of the initial radical are combined into a single step. In methods that employ an external reagent (such as tin hydride), these functions are

accomplished in two separate steps. The transfer of X must be relatively rapid so that standard radical termination or polymerisation reactions cannot compete.

### 1.11.1 Hydrogen atom transfer.

Both hydrogen and halogen atom transfer reactions are possible. Early studies by Julia on hydrogen atom transfer cyclisations have contributed much to the present understanding of the kinetic and thermodynamic factors controlling free radical cyclisations.<sup>46</sup> Julia found that treatment of activated hexenyl derivatives (11) with peroxide initiators gave mixtures of cyclopentane and cyclohexane products (12) and (13) (scheme 17).

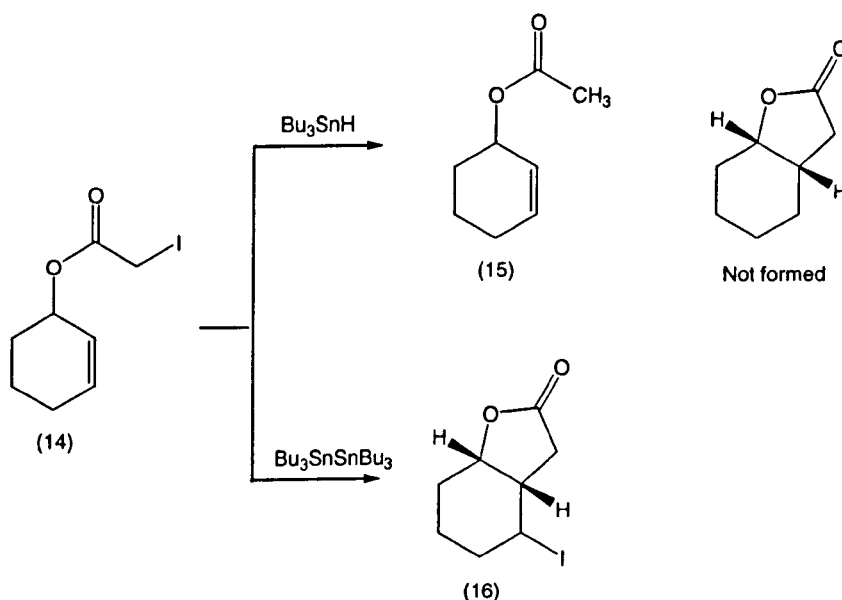


**Scheme 17. Hydrogen atom transfer cyclisation.**

However, large amounts of initiator are generally required and in some cases, a non-chain mechanism may predominate since even the most activated C-H bonds are barely reactive enough to maintain a viable chain reaction. In addition, the hydrogen atom transfer approach results in a reductively terminated reaction, which is of limited synthetic benefit.<sup>47</sup>

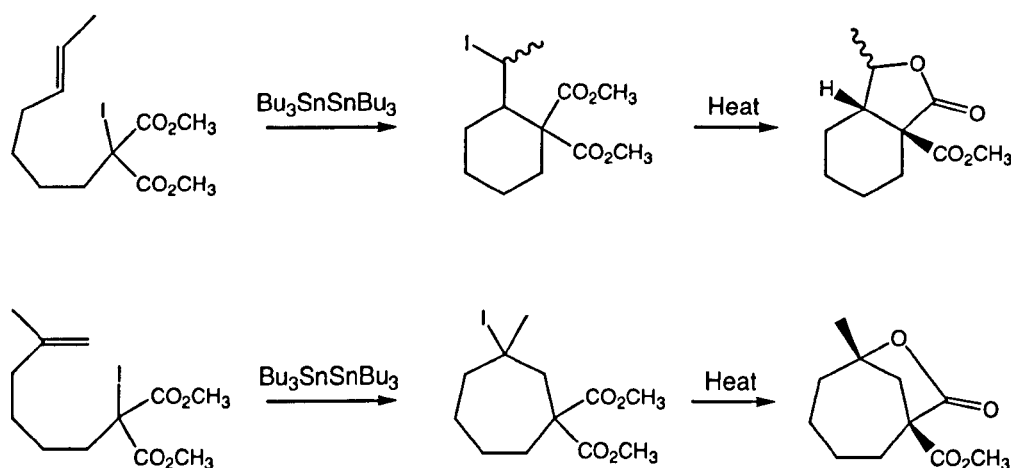
### 1.11.2 Halogen atom transfer.

In comparison, halogen atom transfer reactions have much scope for synthetic development. This method often permits initial and intermediate radicals long lifetimes with respect to chain transfer, allowing relatively slow reactions to occur. This situation cannot occur in the tin hydride method, since all radicals have similar lifetimes with respect to chain transfer. This is illustrated in an example reported by Chang.<sup>48</sup> Thus, attempted cyclisation of iodo ester (**14**) with  $\text{Bu}_3\text{SnH}$  provided the reduction product (**15**) only. However, ditin-mediated halogen atom transfer cyclisation of (**14**) at high concentration (0.3M) gave lactone (**16**) in 55% yield (scheme 18).



Scheme 18. Ditin mediated halogen atom transfer cyclisation of iodo ester (**14**).

In the tin hydride method, the slow cyclisation of the initial radical cannot compete with hydrogen atom abstraction, even at low  $\text{Bu}_3\text{SnH}$  concentrations. However, under atom transfer conditions the same radical is permitted a much longer lifetime. Hence rapid iodine atom transfer from (14) produces lactone (16). Further work by Curran and Chang has demonstrated that the ditin-mediated atom transfer cyclisation of stabilised radicals provides the ability to generate ring sizes other than 5-membered (scheme 19).<sup>49</sup>



**Scheme 19. Ditin-mediated atom transfer radical cyclisation.**

Thus, the relatively slow cyclisations possible atom transfer conditions allow both 6-*exo* and 7-*endo* ditin-mediated reactions to be conducted. The halogen atom transfer cyclisation method therefore provides a valuable area for synthetic application. In addition, a versatile halogen is retained in the product under these conditions, allowing unique and powerful synthetic sequences to be designed using this approach.

## 1.12 Transition metal mediated halogen atom transfer reactions.

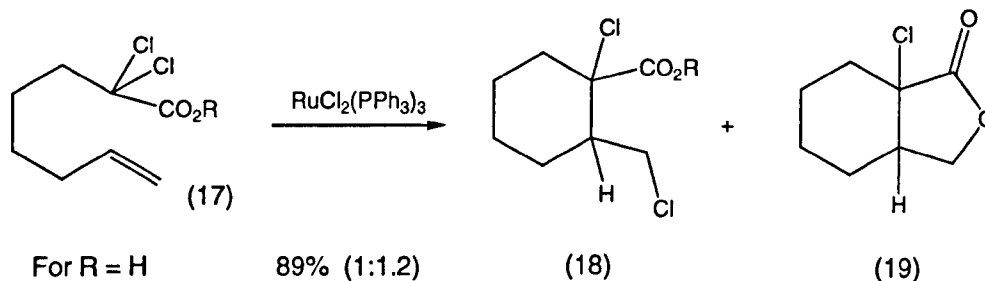
Over the last decade transition metal promoted atom transfer radical reactions have emerged as a viable alternative to stannane based radical chemistry. This is largely due to the pioneering work of Kharasch<sup>45c</sup> and others.<sup>50</sup> Transition metal mediated atom transfer processes are non-reductive and reactions are usually terminated with inclusion of functionality in the product. In addition, reaction work-up is not complicated by the removal of the toxic tin by-products that are associated with traditional stannane based procedures. The advantages of transition metal promoted reactions have led to much research activity in this field. As a result transition metal mediated radical reactions have emerged as important synthetic methods for carbon-carbon bond formation. The most popular types of reagent are those based upon ruthenium, iron and copper although numerous other metals have also been utilised.<sup>51</sup>

### 1.12.1 Ruthenium complexes.

The synthetic utility of radical reactions *via* the interaction of dichlorotris(triphenyl phosphine) ruthenium(II) with an organic halide has found widespread use in organic synthesis. The Ru(II) catalysed addition of polychloroacetic acid to alkenes is a high yielding reaction. In the hands of Matsumoto<sup>52</sup> and others this reaction was found to be particularly useful for additions involving polymerisable olefins such as styrene and methyl methacrylate. The intramolecular version of this reaction has been utilised by Weinreb<sup>53</sup> for the preparation of  $\gamma$ -halocarboxyl and  $\gamma$ -lactones. Thus, dihalo ester (17)

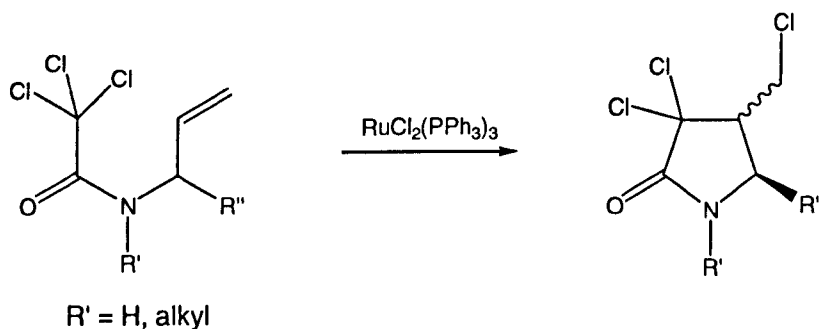


can be efficiently transformed *via* *exo* closure of a 5-hexenyl-type radical to afford both (18) and (19) (scheme 20).



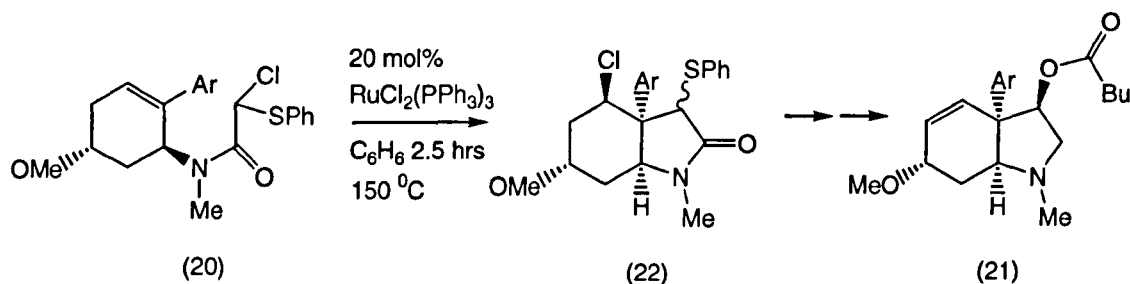
**Scheme 20. Ruthenium mediated cyclisation of dihaloesters.**

Itoh extended the utility of the  $\text{RuCl}_2(\text{PPh}_3)_3$  catalyst by application to synthesis of  $\gamma$ -lactams<sup>54</sup> from both secondary and tertiary amides as shown in scheme 21.



**Scheme 21. Ru(II) mediated cyclisation of trichloroacetamides.**

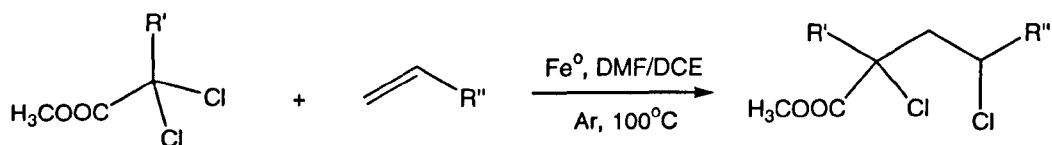
In addition, the precursor (**21**) (for the total synthesis of pretazettine (**22**)) has been prepared in 57% yield by  $\text{RuCl}_2(\text{PPh}_3)_3$  mediated atom transfer cyclisation of chloroacetamide (**20**) (scheme 22).<sup>55</sup>



**Scheme 22. Synthesis of pretazettine *via* Ru(II) mediated cyclisation.**

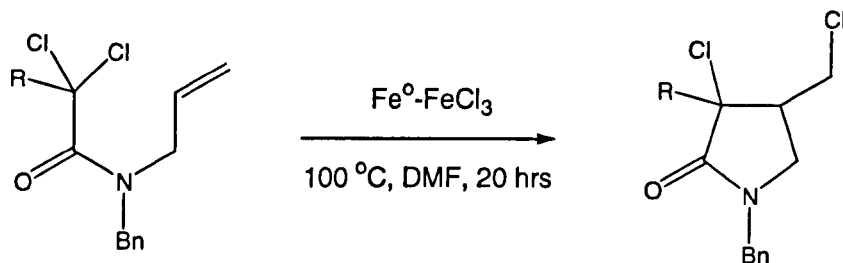
### 1.12.2 Iron complexes.

Halogen atom transfer additions of  $\alpha$ -haloesters to alkenes have been widely investigated and more recently the use of environmentally friendly reagents for this purpose has attracted much interest. Ghelfi and co-workers reported that halogen atom transfer radical additions of methyl 2,2-dichlorocarboxylates to alkenes are efficiently promoted by iron filings (scheme 23).<sup>56</sup>



**Scheme 23.  $\text{Fe}^0$  promoted radical addition to alkenes.**

In a continuation of this work  $\text{Fe}^0\text{-FeCl}_3$  has been shown to mediate cyclisation of *N*-allyl-*N*-benzyl-dichloroacetamides to 2-pyrrolidinones in good yields (scheme 24).<sup>57</sup>

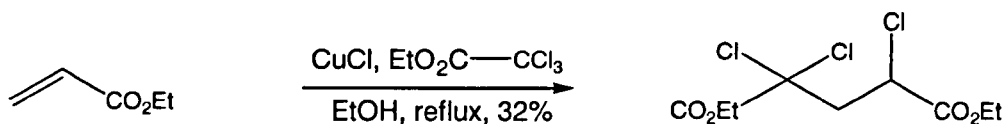


**Scheme 24.  $\text{Fe}^0\text{-FeCl}_3$  promoted preparation of 2-pyrrolidinones.**

More recently the use of iron in the form of  $\text{Fe(II)}$  tris-pyridine-2-ylmethyl-amine has been utilised in the synthesis of various lactones under milder reaction conditions.<sup>58</sup>

### 1.12.3 Copper Complexes.

The most successful transition metal catalysts for atom transfer radical additions are those derived from copper(I)-based halogen compounds.<sup>51</sup> The  $\text{CuCl}$  catalysed intermolecular addition of polyhalocarbons to alkenes has been known for some time (scheme 25).<sup>59</sup> The intramolecular version of this reaction can provide rapid and convenient access to a variety of cyclic systems.

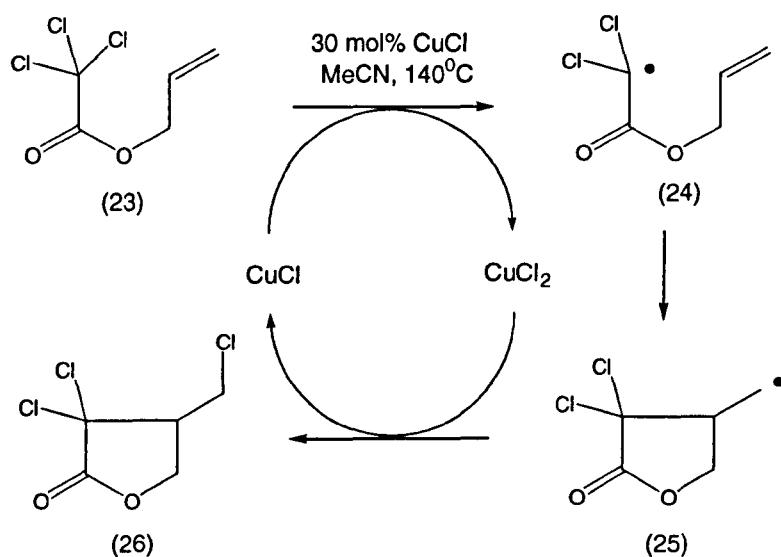


**Scheme 25. copper catalysed intermolecular addition reaction.**

In comparison to alternative reductive methods, the use of copper mediated radical cyclisations has a number of advantages including: the efficient catalytic nature of the process, the low cost of copper halides and the ease of separation of copper complexes from reaction products.

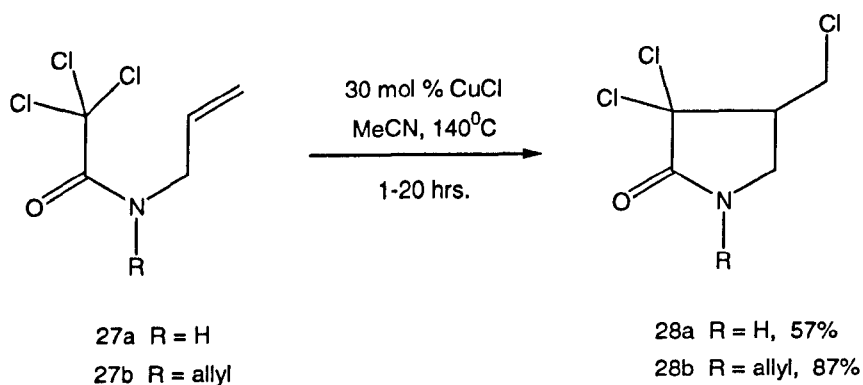
#### 1.12.3.1 Reactions using $\text{CuCl}$ .

Itoh has demonstrated that copper-based oxidative atom transfer cyclisations of activated trichloroacetates<sup>60</sup> involve a redox reaction between copper(I) and copper(II) salts. As shown in scheme 26,  $\text{CuCl}$  formally abstracts a chlorine atom from trichloroacetate (**23**) which generates the initial radical (**24**) and  $\text{CuCl}_2$ . Following 5-*exo* ring closure the newly formed primary radical (**25**) reacts with the  $\text{CuCl}_2$  to regenerate the  $\text{CuCl}$  catalyst and furnish the cyclised product (**26**).



**Scheme 26.** copper(I) mediated atom transfer radical cyclisation.

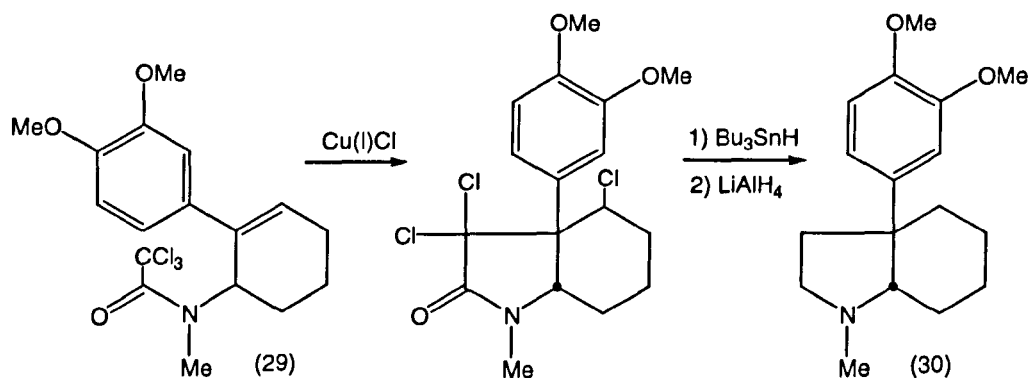
Atom transfer radical cyclisations mediated by CuCl have also been utilised by Itoh for the preparation of  $\gamma$ -lactams.<sup>54,61</sup> Thus, reaction of trichloroacetamides **27a-b** with a catalytic amount of CuCl in MeCN at 140°C afford the 5-*exo* atom transfer products **28a-b** (scheme 27).



**Scheme 27.** Copper(I) mediated radical cyclisation of trichloroacetamides.

Using this methodology the cyclisation of both secondary **27a** and tertiary **27b** amides were possible. Note that cyclisation of the tertiary amide was the more efficient and that no products arising from 6-*endo* closure were detected.

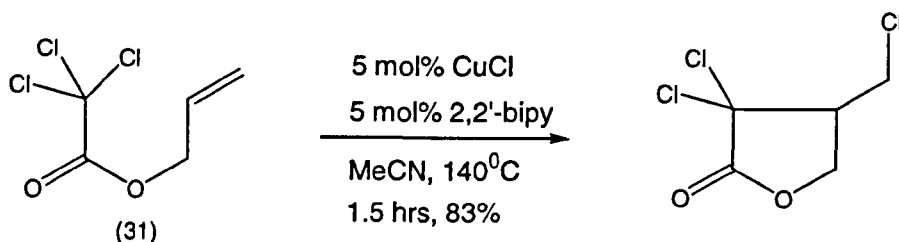
Bicyclic lactams which possess pyrrolidine alkaloid skeletons are readily prepared using this approach. Accordingly, mesembrane (**30**) has been synthesised<sup>61</sup> in 47% yield by CuCl catalysed cyclisation of *N*-allyl-trichloroacetamide (**29**) (scheme 28).



**Scheme 28. Preparation of mesembrane via CuCl mediated radical cyclisation.**

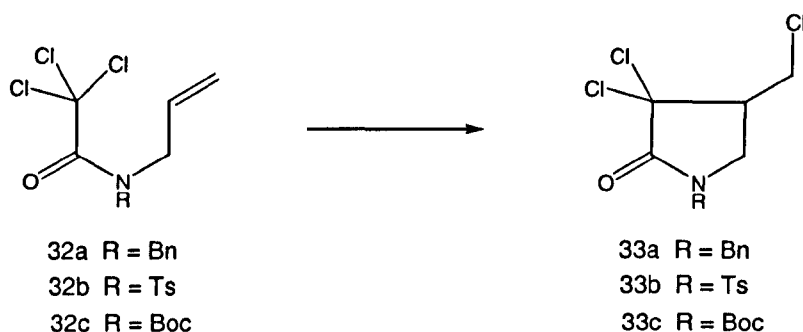
### 1.12.3.2 The use of copper halide : 2,2'-bipyridine complexes.

Itoh screened a range of copper salts as potential catalysts<sup>62</sup> and found that a number of compounds were effective in mediating the cyclisation of trichloroacetate (**31**) (scheme 29). However, the addition of an equimolar amount of 2,2'-bipyridine (bipy) to CuCl resulted in a marked increase in the rate of reaction.



**Scheme 29.** CuCl:bipy promoted cyclisation of trichloroacetate (31).

Further work in this field has demonstrated that in general the addition of either amine or pyridine-based ligands causes rapid rate enhancements for a variety of cyclisation and intermolecular addition reactions.<sup>62</sup> Thus, reaction of substrates **32a-c** (table 2) shows that CuCl:bipy catalysed the cyclisation more rapidly than CuCl alone.<sup>63</sup>

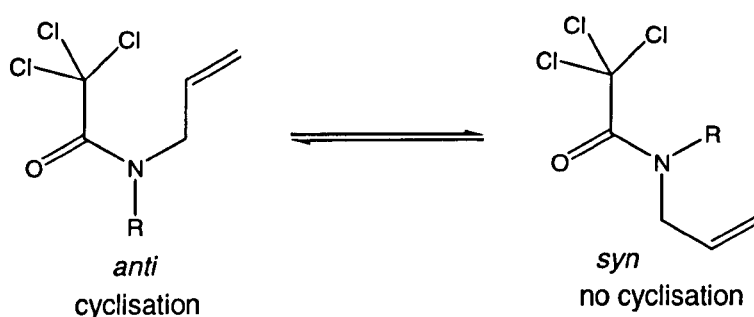


Substrate	Catalyst (mol%)	Temp (°C)	Time (hrs)	Yields (%)
32a	CuCl (30)	80	18	68
32a	CuCl : bipy (30)	RT	1	98
32b	CuCl (30)	RT	24	97
32b	CuCl : bipy (5)	RT	0.2	91
32c	CuCl (30)	80	4	80
32c	CuCl : bipy (30)	RT	2	78

Reactions with CuCl were run in MeCN, reactions with CuCl(bipy) were run in DCM.

**Table 2** Effect of catalyst and protecting group on cyclisation of trichloroacetamides

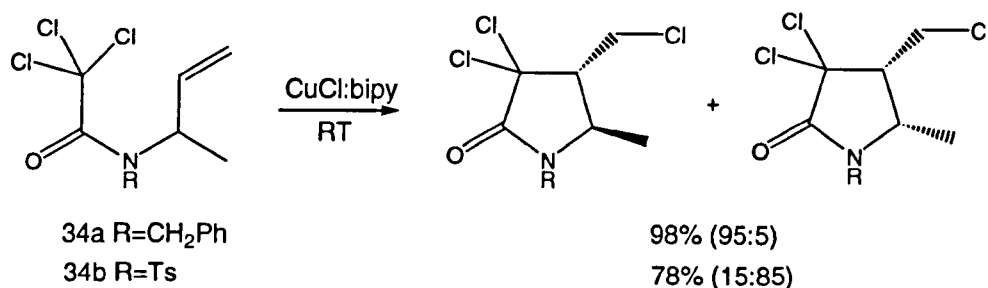
Ligands such as 2,2'-bipyridine accelerate the atom transfer process by solubilising the CuCl and by altering the redox potential of the catalyst system. Thus, the use of more activated catalysts often permit cyclisations to be conducted at room temperature (table 2). The nature of the *N*-protecting group was also found to influence the rate of cyclisation. In general, bulky or electron withdrawing *N*-protecting groups (**32b-c**) facilitate cyclisation by altering the conformational population of the substrate in favour of the *anti* conformer (scheme 30).<sup>64</sup>



**Scheme 30. conformations of the amide bond.**

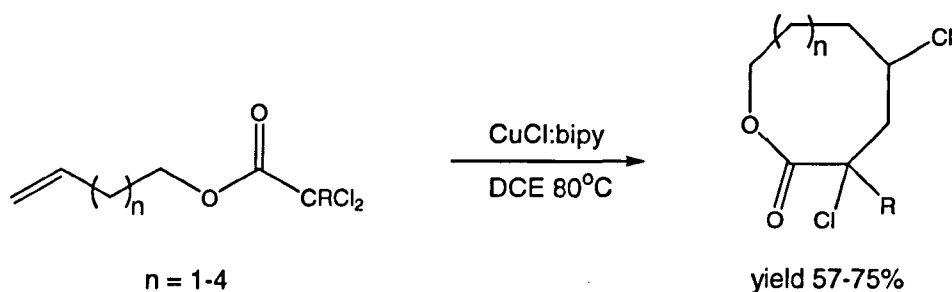
Stereoselectivities of the CuCl:bipy-catalysed 5-*exo* cyclisation of trichloroacetamides **34a-b** were also found to be dependant on the protecting group. Cyclisation of *N*-benzyl- (**34a**) and *N*-methyl-*N*-allyl-trichloroacetamide furnished the corresponding *trans* isomer as the major product. In contrast, cyclisation of the *N*-tosyl (**34b**), *N*-mesyl, *N*-Cbz and *N*-Boc analogues predominantly afforded the *cis* isomer (scheme 31).<sup>63</sup>





**Scheme 31. Effect of protecting group on stereochemical outcome of reaction.**

The highly active CuCl:bipy catalyst system permits cyclisation of mono-halo substrates, albeit at elevated temperatures (~80°C).<sup>65</sup> In addition, Speckamp has demonstrated that medium sized lactones can be efficiently prepared by CuCl:bipy mediated cyclisation of di- and trichloroacetates (scheme 32).<sup>66</sup>



**Scheme 32. CuCl:bipy mediated macrocyclisations.**

The efficiency of these medium ring cyclisations coupled with the inability of Bu<sub>3</sub>SnH based procedures to facilitate such reactions has prompted suggestion that reactions may proceed *via* a copper templating process.<sup>66</sup> Despite the versatility of CuCl:bipy mediated cyclisations, large amounts of catalyst are often required (typically 30 mol%), and

formation of larger rings (10-12 membered) is not possible without rigid structural control.<sup>66</sup>

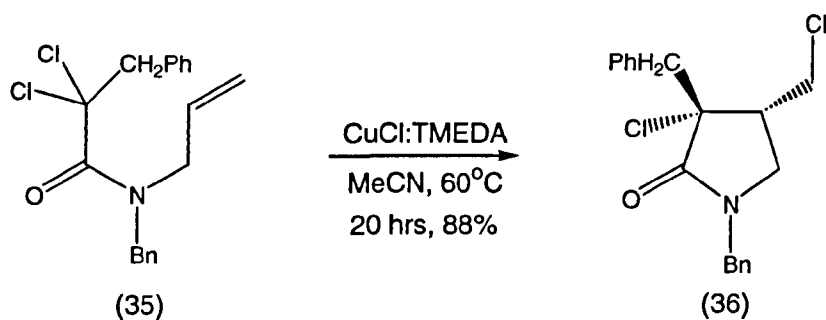
### 1.12.3.3 The second generation of copper based catalysts.

The ability to modify both the solubility and redox potential of atom transfer catalysts by introducing a ligand has prompted much activity in the use of alternative ligand systems for cyclisation reactions. The discovery that different ligands can govern the reactivity, yield and selectivity of atom transfer cyclisations has resulted in the preparation of a range of highly activated catalysts and has greatly expanded the scope of this methodology.

#### 1.12.3.3a *N,N,N',N'*-Tetramethylethylenediamine (TMEDA).

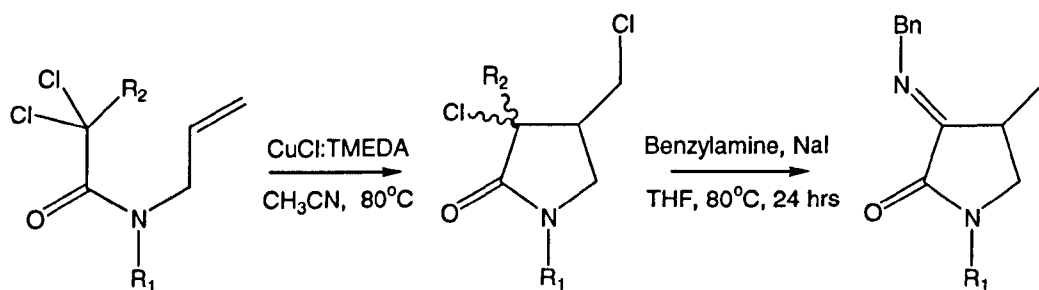
Ghelfi has reported the use of CuCl:TMEDA as an efficient promoter for atom transfer radical cyclisation reactions.<sup>67</sup> Compared to the classic CuCl:bipy reagent combination, improved yields at lower catalyst concentrations were obtained. In addition, cyclisations were often conducted at lower temperatures using this highly active system.

Thus, cyclisation of **(35)** with 10 mol% CuCl(TMEDA)<sub>2</sub> at 60°C furnished **(36)** as a single diastereomer in 88% yield (scheme 33).<sup>67</sup> Note that attempts to cyclise **(35)** using CuCl:bipy failed, emphasising the importance of the correct choice of ligand.



**Scheme 33.  $\text{CuCl(TMEDA)}_2$  mediated cyclisation of dichloroacetamide (35).**

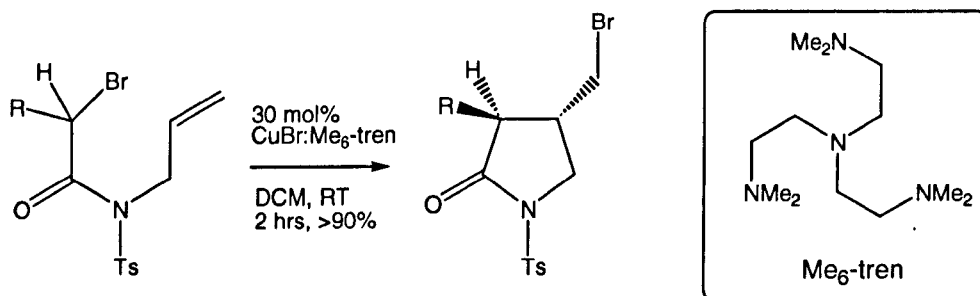
The synthetic utility of  $\text{CuCl:TMEDA}$  mediated cyclisations has been demonstrated further by application to the total synthesis of pilolactam<sup>68</sup> and in the preparation of biologically interesting 3-benzylimino-2-pyrrolidinones (scheme 34).<sup>69</sup>



**Scheme 34.  $\text{CuCl:TMEDA}$  promoted synthesis of 3-benzylimino-2-pyrrolidinones.**

### 1.12.3.3b *N,N,N',N',N'',N''*-hexamethyltriethylenetetramine (Me<sub>6</sub>-tren).

Ghelfi reported that two equivalents of bidentate TMEDA : copper halide were required for optimum activity.<sup>67</sup> As a direct consequence of this observation a number of multidentate amine ligands have been investigated as potential catalysts for ATRC reactions. The most successful polydentate amine ligand of those screened was found to be the tetradentate Me<sub>6</sub>-tren ligand.<sup>70</sup> Thus, the use of a 1:1 ratio of copper halide:Me<sub>6</sub>-tren in a variety of solvents has enabled a range of monohalo substrates to be cyclised at room temperature (scheme 35).

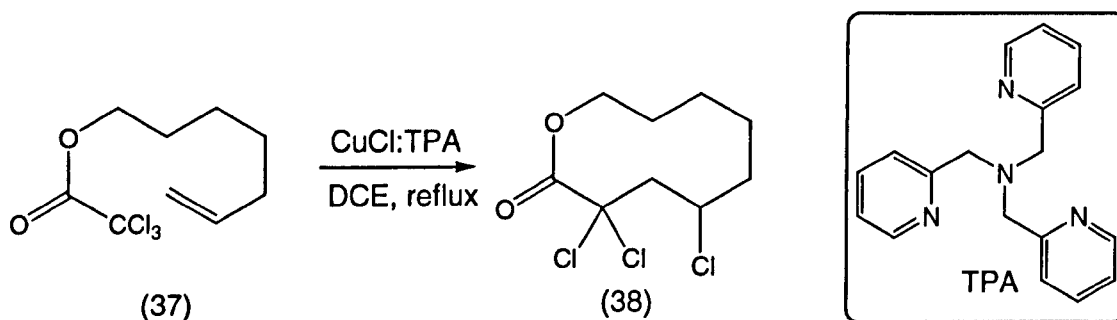


**Scheme 35. CuBr:Me<sub>6</sub>-tren promoted cyclisation of monobromoacetamides.**

The use of this catalyst system has also enabled the formation of bicyclic lactams *via* the less common 5-*endo* mode of cyclisation (section 1.5.2.2). Using this extremely active catalyst system it is not necessary to use dried glassware or solvents. In addition, a facile work-up procedure often provides cyclised products without the need for purification.

**1.12.3.3c Tris-(2-pyridyl-methyl)-amine (TPA).**

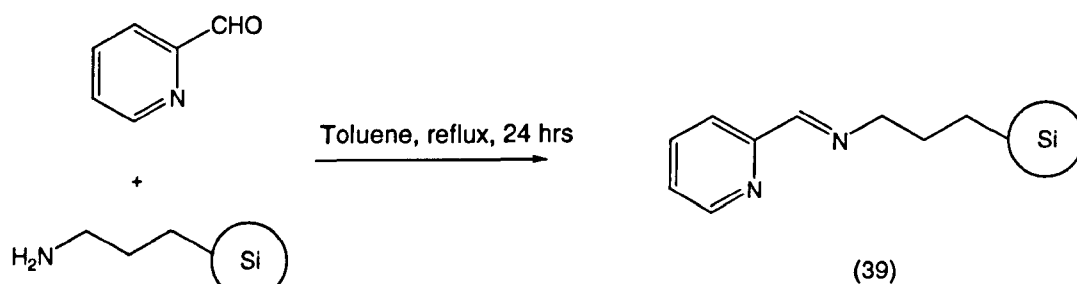
Verlhac and co-workers recently reported that multidentate pyridine ligands were successful in mediating a range of macrocyclisation reactions.<sup>58</sup> The employment of this ligand system has enabled macrocyclisations that were previously impossible using the copper halide:bipy derived catalyst. For example, reaction of (37) with 10 mol% CuCl:TPA afforded (38) in 70% yield (scheme 36). In addition, this versatile approach has been utilised for the preparation of a range of crown ethers<sup>71</sup> and  $\delta$ -lactams.<sup>70a</sup>



**Scheme 36. CuCl:TPA mediated macrocyclisation reaction.**

#### 1.12.3.4 Solid supported copper(I) atom transfer catalysts.

In order to develop re-usable atom transfer catalysts the immobilisation of pyridine-imine ligands onto solid supports has been investigated within the Clark group.<sup>72</sup> Thus, reaction of pyridine-2-carboxaldehyde with aminopropylated silica followed by stirring with a solution of copper halide furnished the catalyst **(39)** (scheme 37).

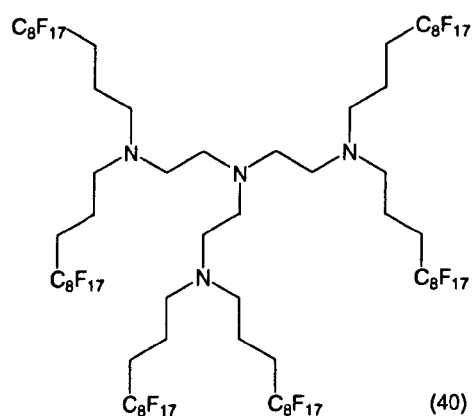


**Scheme 37. Synthesis of solid supported ligand.**

The catalyst was active in both *5-exo* and *5-endo* atom transfer radical cyclisation of a range of haloacetamide substrates. However, the supported catalyst was less active than its equivalent homogenous counterpart (which will be discussed in detail in chapter 2). Upon re-use, a decrease in activity of the supported catalyst system was observed. This was found to be due not to leeching of the copper from the polymer bound catalysts, but due to the formation of an inactive copper dihalide complex.

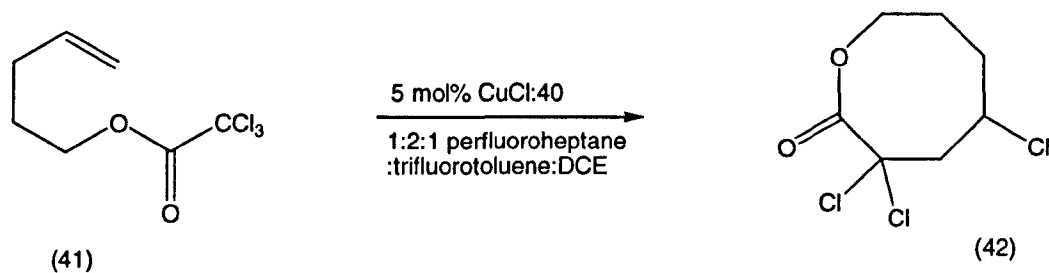
### 1.12.3.5 Perfluorous substituted atom transfer cyclisation catalysts.

The use of perfluorous catalysis in a variety of organic reactions has been developed. In general, two phases are used in the reactions (a perfluorous solvent and an organic solvent). Hence, in this approach the perfluorous catalyst is confined to the perfluorous phase while the organic reactants and products are confined to the organic phase. However, at elevated temperatures the two phases are miscible allowing the desired reaction to be catalysed. Upon completion, the reaction is cooled (normally to ambient temperature) and the phases again become immiscible allowing easy separation of products from catalysts. The perfluorinated analogue (40) of the Me<sub>6</sub>-tren ligand (section 1.12.3.3b) was shown to be soluble in perfluorocyclohexane.<sup>73</sup>



The ligand was used as a 1:1 mixture with CuCl and screened in the macrocyclisation of trichloroester (41) (scheme 38). Cyclisation was slower using (40) in the perfluorous solvent than the corresponding Me<sub>6</sub>-tren system under conventional atom transfer

conditions. However, reaction of **(41)** with 5 mol% CuCl(40) afforded **(42)** after 10 hours in 97% yield.



**Scheme 38. Macrocyclisation using perfluorous catalysis.**

Recycling of the catalyst is possible by simple decantation of the perfluorous layer. In addition, the inertness of most perfluorous solvents further increases the attractiveness of this relatively environmentally friendly methodology.



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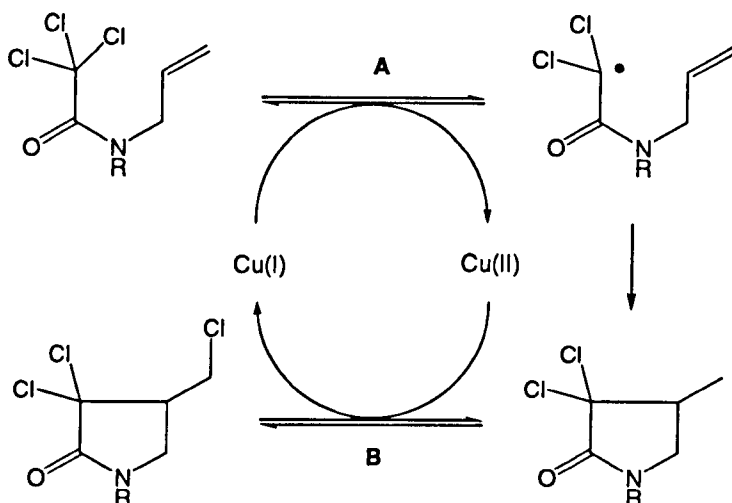
## **Chapter 2**

# **Ligand Electronic Effects On Rates Of Copper Mediated Atom Transfer Radical Cyclisation And Polymerisation**

### **2.1 Introduction.**

The use of transition metal complexes to mediate atom transfer radical cyclisation (ATRC) and atom transfer radical polymerisation (ATRP)<sup>1</sup> has attracted much interest in recent years. Radical cyclisations of *N*-allylhaloacetamides with a range of transition metal based catalysts including (RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>)<sup>2</sup>, FeCl<sub>2</sub>(P(OEt)<sub>3</sub>)<sub>3</sub>,<sup>3</sup> CuCl(Bipy),<sup>4</sup> CuCl(TMEDA)<sub>2</sub><sup>5</sup> and CuCl(*N,N,N',N',N''*-pentamethyltriethylenetetramine)<sup>6</sup> have been reported. However, even with these catalysts elevated temperatures and highly activated carbon-halogen bonds (e.g.  $\alpha,\alpha,\alpha$ -trihaloacetyls) are often required. By far the most successful systems are those derived from copper(I) halogen compounds and the most widely used catalysts, particularly for ATRP are based upon bipyridine ligands. Improving catalytic efficiency should result in increased yields at lower temperatures and permit the cyclisation of less activated monohaloacetamide precursors. To enhance the rate of catalysis it would be necessary to alter the redox potential of the system thus

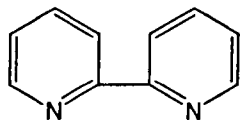
influencing the equilibrium A and B (scheme 39). This may be achieved by variation of the copper ligand.



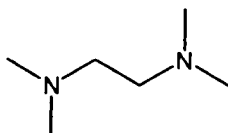
**Scheme 39. Mechanism of copper(I) mediated atom transfer radical cyclisation.**

By preparing analogues to the bipyridine system Matyjaszewski<sup>7</sup> has demonstrated that it is possible to alter both the solubility and electronic effects of complexes and consequently affect the position of equilibrium, thus allowing for limited control over the rate of product formation. However, while a range of different catalyst systems have been investigated no study on the modification of existing ligands has been undertaken in order to elucidate structure activity relationships. This is probably due to the inherent synthetic difficulties associated with the chemical modification of ligands such as bipyridine<sup>8</sup> (**43**) and TMEDA (**44**). Consequently a related class of ligand (**45**) was selected for investigation as a potentially tunable synthetic alternative to bipyridine.

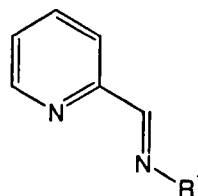




(43)



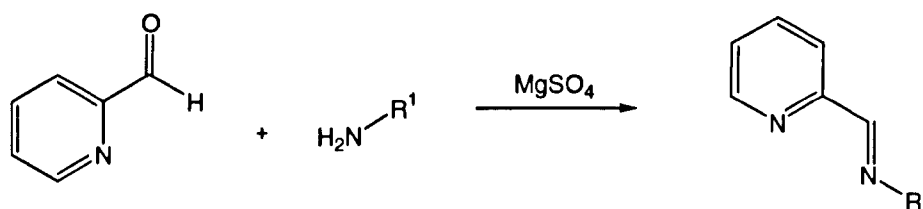
(44)



(45)

Like bipyridine (43), *N*-alkyl-2-pyridylmethanimine (NPMI) (45) ligands have a conjugated  $\pi$  system which is able to accept electron density from the metal thus serving to stabilise the Cu(I) oxidation state. In fact NPMI ligands have been reported to be superior to bipyridine in both stabilising and solubilising copper(I) halides.<sup>9</sup>

These ligands are readily prepared by reaction of commercially available amines with pyridine carboxaldehydes in the presence of  $\text{MgSO}_4$  (scheme 40). Therefore a wide range of structurally related ligands can be prepared and assessed as atom transfer catalysts enabling structure activity relationships to be obtained.

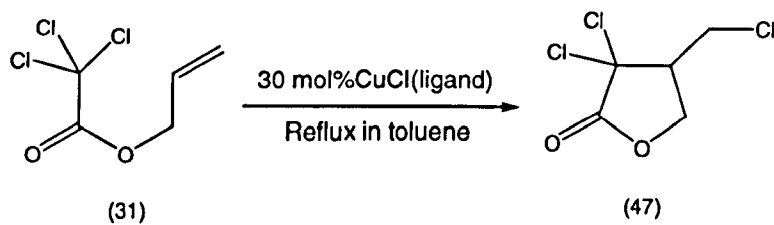


**Scheme 40. Preparation of *N*-alkyl-2-pyridylmethanimines.**

## 2.2 Work previously conducted within the Clark group.

### 2.2.1 Efficiency of the CuCl(*N*-alkyl-2-pyridylmethanimine) catalyst.

Initial work to determine the efficiency of the copper complex of this ligand focussed on the known cyclisation of trichloroallylacetate (**31**). Hence cyclisation of (**31**) under atom transfer conditions with 30 mol% CuCl and 30 mol% of either *N*-pentyl-2-pyridylmethanimine (NPMI), TMEDA (**44**) or bipyridine (**43**) as ligand was attempted (table 3).<sup>10</sup>



Ligand	Ratio of (31):(47) <sup>a</sup>
TMEDA	4:1
Bipyridine	5:1
<i>N</i> -Pentyl-2-pyridylmethanimine	1:1

<sup>a</sup> Reactions stopped after 4 hrs.

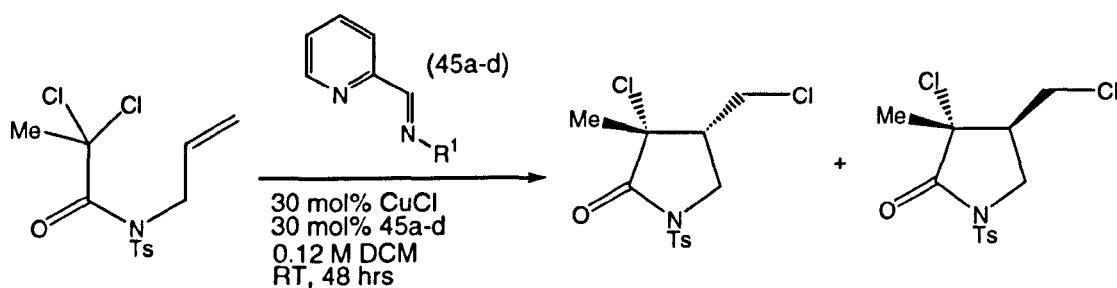
**Table 3. Comparison of ligand efficiency.**

The *N*-pentyl-2-pyridylmethanimine ligand gave a moderate rate enhancement over the other two ligands demonstrating the synthetic potential of this system. Further work within the group has shown that CuCl(NPMI) is also effective in facilitating the atom transfer of both activated and non-activated  $\alpha$ -haloacetamides.<sup>11</sup> Comparisons with

previously reported systems have shown that the NPMI catalyst offers improved yields and greater diastereoselectivities than when using  $\text{RuCl}_2(\text{PPh}_3)_3$ . Reaction rates were comparable with those obtained using the  $\text{CuCl}(\text{TMEDA})_2$  system reported by Ghelfi with high levels of conversion and little or no reduction in selectivity observed. In addition, copper NPMI complexes have been reported to be extremely effective in the atom transfer radical polymerisation of methyl methacrylate<sup>12</sup> further demonstrating the utility of this system.

### 2.2.2 Optimisation of the $\text{CuCl}(\text{N-alkyl-2-pyridylmethanimine})$ catalyst.

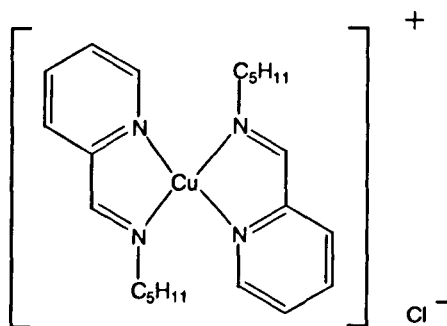
Work within the group has indicated that the steric nature of the imine substituent ( $\text{R}^1$ ) is crucial in controlling the rate and stereoselectivity of cyclisation. Primary substituents gave optimum activity whilst more bulky imine substituents retarded the rate of cyclisation (table 4).<sup>10</sup>



Ligand	$\text{R}_1$ group	Relative rate	Diast. Ratio
45a	<i>n</i> -Bu	45	18:82
45b	<i>i</i> -Bu	28	28:72
45c	<i>s</i> -Bu	3	32:68
45d	<i>t</i> -Bu	1	51:49

Table 4. Effect of imine substituent on cyclisation.

The optimum ratio of bidentate ligand to Cu was found to be 2:1 suggesting the active catalyst to be a four-coordinated complex (48). The X-ray structures of such complexes have been published<sup>9</sup> and indicate a regular tetrahedral arrangement of ligands around the copper.



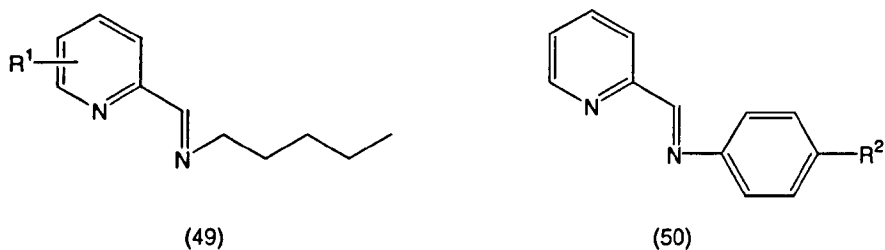
(48)

The difference in rate of cyclisation when using 1:1 and 2:1 ligand:copper was not significant enough to warrant the use of larger amounts of ligand. Hence, all studies are based upon a 1:1 ratio of ligand:copper.

### 2.3 Initial aims.

Our ultimate aim was to investigate how catalyst structure related to activity. Based on the success of the copper(NPMI) system and encouraged by the effect of the imine alkyl group on catalytic activity, we proposed to investigate how electronic effects in this ligand influence reactivity. Therefore, varying the electronic nature of substituents at the pyridine nucleus (R<sup>1</sup>) (49) and investigating the effects of *p*-substituted aromatic imine

substituents ( $R^2$ ) (50) should enable us to determine structure activity relationships for this class of ligand and result in optimising both the ATRC and ATRP processes.

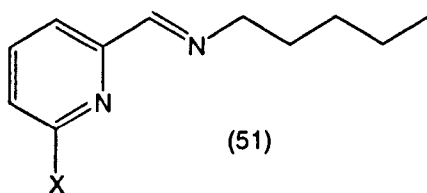


**Scheme 41. Proposed NPMI derivatives for structure activity investigation.**

## 2.4 Ligand synthesis.

### 2.4.1 Synthesis of 6-functionalised *N*-pentyl-2-pyridylmethanimine ligands.

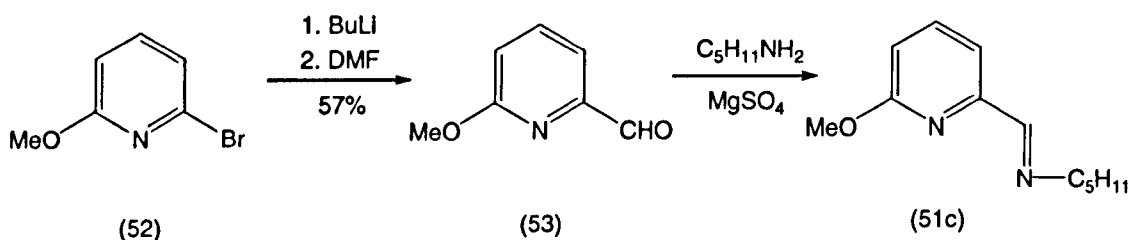
In order to investigate ligand electronic effects on catalytic activity we initially prepared a range of NPMI ligands that were substituted at the 6-position of the pyridine nucleus (51a-c).



51a X=H  
51b X=Me  
51c X=OMe

The preparation of *N*-pentyl-2-pyridylmethanimine (**51a**) and 6-methyl-*N*-pentyl-2-pyridylmethanimine (**51b**) was readily achieved by a facile condensation reaction between the appropriate commercially available pyridinecarboxaldehyde and amyl amine. Thus, to either 2-pyridinecarboxaldehyde or 6-methyl-2-pyridinecarboxaldehyde in diethyl ether containing excess magnesium sulphate was added amyl amine. The mixtures were then stirred overnight at room temperature. Both reactions proceeded cleanly in almost quantitative yield to afford the desired compounds (**51a**) (94%) and (**51b**) (82%). Subsequent purification of the products was unnecessary.

The corresponding 6-methoxy ligand (**51c**) was prepared from 6-bromo-2-methylpyridine (**52**) as described in scheme 42.

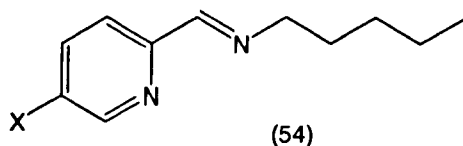


**Scheme 42. Synthesis of 6-methoxy-*N*-pentyl-2-pyridylmethanimine.**

Reaction of 6-bromo-2-methylpyridine (**52**) with BuLi followed by DMF was conducted in accordance to standard literature procedure to afford 6-methoxy-2-pyridinecarboxaldehyde (**53**).<sup>13</sup> Subsequent condensation with amyl amine as described previously then furnished 6-methoxy-*N*-pentyl-2-pyridylmethanimine (**51c**) in 89% yield.

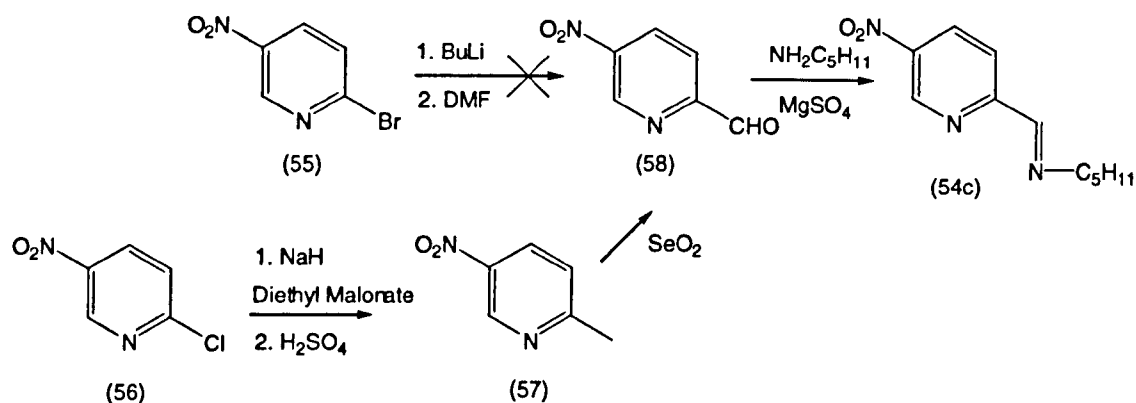
### 2.4.2 Synthesis of 5-functionalised *N*-pentyl-2-pyridylmethanimine ligands.

We next turned our attention to the synthesis of the related class of 5-substituted NPMI ligands (**54a-d**).



54a X=H  
 54b X=Me  
 54c X=NO<sub>2</sub>  
 54d X=OMe

The synthesis of 5-methyl-*N*-pentyl-2-pyridylmethanimine (**54b**) was conducted in a manner analogous to that used for the preparation of the 6-methoxy ligand (**51c**) (section 2.4.1 scheme 42) and resulted in an overall yield of 43% from the starting 2-bromo-5-methoxypyridine. However, a similar approach was found to be unsuitable for the preparation of the corresponding 5-nitro substituted ligand (**54c**). The reaction of 2-bromo-5-nitropyridine (**55**) with BuLi and DMF to give 5-nitro-2-pyridinecarboxaldehyde (**58**) failed. Compounds isolated from the reaction mixture would seem to indicate that the presence of the strongly electron withdrawing NO<sub>2</sub> group facilitated a nucleophilic aromatic substitution reaction resulting in the introduction of butyl groups to the pyridine ring. Therefore an alternative route was utilised in which 5-nitro-2-pyridinecarboxaldehyde (**58**) was prepared in a two step procedure as reported by Ishii<sup>14</sup> (scheme 43).



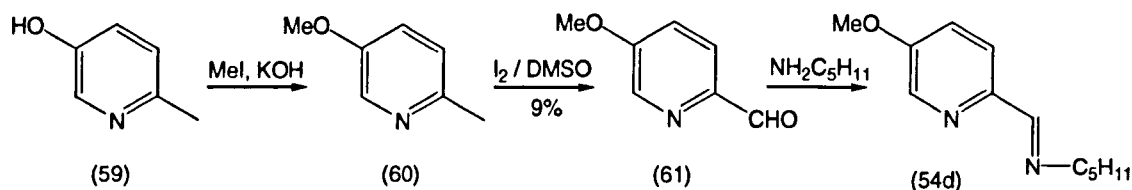
**Scheme 43. Synthesis of 5-nitro-*N*-pentyl-2-pyridylmethanimine (54c).**

This involved using a modification of the procedure of Dummel and Mosher.<sup>15</sup> Thus, NaH was added to a solution of diethyl malonate and after the evolution of hydrogen had subsided 2-chloro-5-nitropyridine (56) was introduced. The solvent was removed and the resultant residue was then refluxed in 6M sulfuric acid for 7 hours to afford 2-methyl-5-nitropyridine (57) in 69% yield. Subsequent oxidation was conducted by refluxing with selenium dioxide in 1,4-dioxane at 110°C for 6.5 hours. Purification by column chromatography furnished 5-nitro-2-pyridinecarboxaldehyde (58) in excellent yield (85%). Reaction with amyl amine as described previously then provided the desired 5-nitro-*N*-pentyl-2-pyridylmethanimine ligand (54c).

The preparation of the 5-methoxy-*N*-pentyl-2-pyridylmethanimine ligand (54d) proceeded *via* the route outlined in scheme 44. The two step synthesis of the key pyridinic aldehyde (61) involved initial O-alkylation of 5-hydroxy-2-methylpyridine (59) followed by oxidation of the methyl group to the carbonyl. The O-alkylation was carried



out using 2 equivalents methyl iodide in DMSO with potassium hydroxide (4 equivalents) as a base. The mixture was stirred at room temperature for 2 hours and 5-methoxy-2-methylpyridine (**60**) was then isolated in 50% yield using column chromatography.



**Scheme 44. Synthesis of 5-methoxy-N-pentyl-2-pyridylmethanimine (54d).**

To oxidise 5-methoxy-2-methylpyridine (**60**) to 5-methoxy-2-pyridinecarboxaldehyde (**61**) we employed the method reported by Markovac and others<sup>16</sup> in which oxidation is brought about by attack of iodine and dimethylsulfoxide. The resultant pyridinic aldehyde (**61**) is reported to be unstable at room temperature and highly susceptible to decomposition,<sup>17</sup> which may account for the poor yield obtained. A simple condensation reaction then provided the target ligand (**54d**).

#### 2.4.3 Synthesis of *p*-substituted phenyl-pyridin-2-ylmethyleamine ligands.

A range of *p*-substituted phenyl-pyridin-2-ylmethyleamine ligands (**64a-d**) were readily prepared in one step from the corresponding phenyl amine (**63a-d**) and 2-pyridinecarboxaldehyde (**62**).

Hence, aniline, *p*-toluidine, *p*-anisidine and 4-aminobenzotrifluoride were each stirred with 2-pyridinecarboxaldehyde (62) in dry dichloromethane containing excess magnesium sulfate overnight at room temperature. The magnesium sulfate was removed by filtration and the solvent removed under reduced pressure to provide the desired ligands without the need for further purification (table 5).

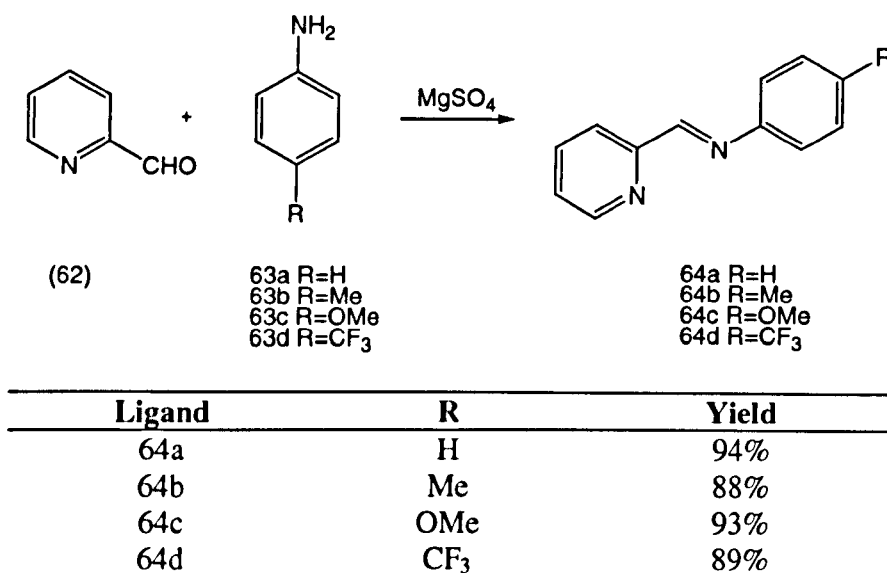
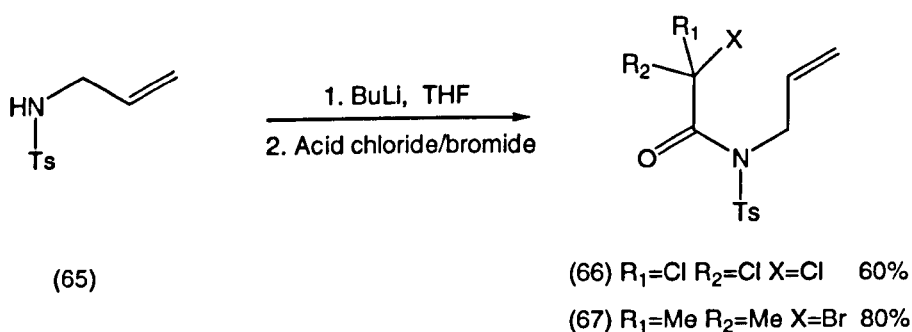


Table 5. Synthesis of ligands 64a-d.

## 2.5 Precursor synthesis.

With a range of modified ligands now in hand we turned our attention to the synthesis of the radical cyclisation precursors. The majority of published atom transfer procedures utilise activated trihaloacetamide precursors. Therefore, *N*-allyl-*N*-toluenesulfonyl-2,2,2-trichloroacetamide (66) was selected for preparation. However, the generation of highly functionalised cyclic systems has limitations in the preparation of natural products. The

inclusion of too many halogen atoms usually necessitates a dehalogenation reaction later in the synthesis. Therefore, a truly versatile atom transfer procedure should provide the ability to generate radicals from non-activated monohalo precursors and without the requirement of elevated temperatures. Consequently *N*-allyl-*N*-(2-bromo-2-methylpropionyl)toluene-*p*-sulfonamide (**67**) was selected as our standard substrate with which to initially assess the modified ligands. The preparation of the selected cyclisation precursors (**66-67**) was conducted according to standard literature procedures. Thus, a solution of BuLi was added dropwise over a period of 5 minutes to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (**65**) (previously prepared by literature procedure) in dry THF at -78°C under an atmosphere of nitrogen. The mixture was stirred for 30 minutes at this temperature, the appropriate acid halide was then introduced and the mixture stirred for a further 3 hours (scheme 45). Following work-up purification by column chromatography afforded the desired compounds in moderate to good yield.



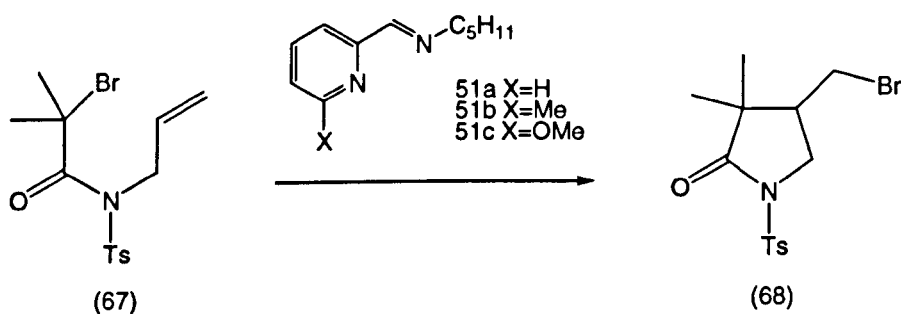
**Scheme 45. Synthesis of *N*-allyl-*N*-toluenesulfonyl-*N*-tri and mono-haloacetamides.**

## 2.6 Atom transfer radical cyclisation reactions.

In order to obtain comparable rate data for cyclisation reactions using our modified ligands a standard experimental procedure was adopted. Thus, cyclisations were conducted at ambient temperature under an atmosphere of nitrogen and all reactions were run at 0.12 M concentration in order to be consistent with previous work. The copper complex of the appropriate ligand was formed in solution before being added to the substrate. In all cases the atom transfer catalyst formed immediately and appeared as a dark brown solution.

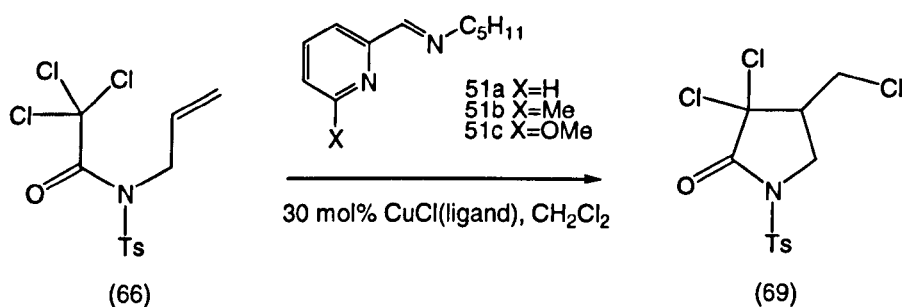
### 2.6.1 Copper mediated ATRC using 6-functionalised NPMI ligands.

Initial reactions were carried out using *N*-allyl-*N*-(2-bromo-2-methylpropionyl)toluene-*p*-sulfonamide (**67**) in dichloromethane (0.12 M) at room temperature with 30 mol% CuBr and 30 mol% of ligand (**51a-c**) (scheme 46).



Scheme 46. ATRC of **67** mediated by CuBr(**51a-c**).

However, attempted cyclisation of (67) using ligands (51b-c) failed with only starting material being recovered after 24 hours. By comparison, the control ligand (51a) mediated the cyclisation of (67) under identical conditions to afford 4-bromomethyl-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (68) in 96% yield in 24 hours. This poor activity prompted us to repeat the screening of ligands (51a-c) using the more activated trichloroacetamide substrate (66). Thus, reactions were conducted as described above but using CuCl instead of CuBr (scheme 47).



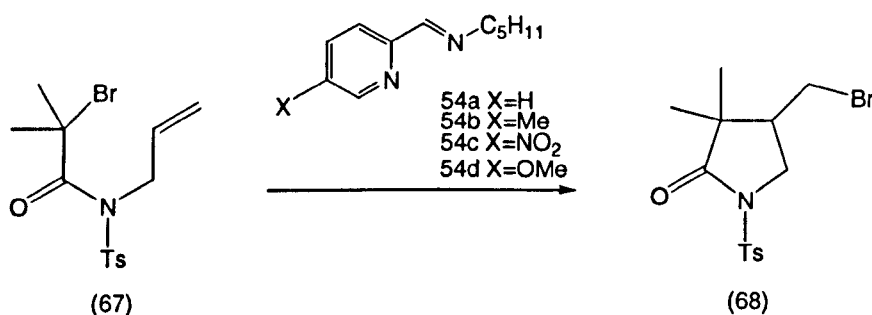
**Scheme 47. ATRC of 66 mediated by CuCl(51a-c).**

After 100 minutes the reactions were worked up by passing the reaction mixture through a small silica plug using dichloromethane as eluent. Conversions were then measured from the <sup>1</sup>H NMR of the crude reaction mixture. Analysis indicated that while the reaction mediated by the 6-methoxy ligand (51c) had gone to completion, reaction using (51b) proceeded to give only a 2:1 mixture of (69):(66). By comparison cyclisation of (66) with the control ligand (51a) was complete in less than 5 minutes under the same conditions. These results indicate that substitution at the 6-position of the pyridine nucleus significantly retards the cyclisation reaction. The reason for this is likely to be

steric in origin and parallels the loss of reactivity observed when the imine nitrogen was substituted with bulky alkyl groups.<sup>10</sup>

### 2.6.2 Copper mediated ATRC using 5-functionalised NPMI ligands.

Due to the relative inactivity of the 6-functionalised analogues (section 2.6.1) we next investigated the affect of NPMI ligands substituted at the 5-position. With the use of ligands (**54a-d**) steric interactions would be less significant allowing contributions from inductive electronic effects onto the pyridine nitrogen to be determined. However, groups in the 5-position are also mesomerically linked to the imine nitrogen and hence analysis of the effect of substituents is likely to be complicated by a combination of both these phenomena. Reactions were carried out using (**67**) in dichloromethane (0.12 M) at room temperature with 30 mol% CuBr and 30 mol% of ligand (**54a-d**) (scheme 48).



**Scheme 48. Investigation of affect of ligands (54a-d).**

After 2 hours the reactions were worked up as described before and the conversion determined from the crude <sup>1</sup>H NMR (table 6).

Ligand	Mass Balance (%)	Ratio 67:68
54a	95	41:59
54b	96	34:66
54c	96	100:0
54d	95	73:27

**Table 6. Cyclisation of 67: effect of ligand on conversion.**

The strongly electron withdrawing NO<sub>2</sub> group (ligand **54c**) had a marked effect on the conversion of (**67**) with no cyclisation product (**68**) detected after 2 hours. The use of the less inductively withdrawing methoxy ligand (**54d**) also retarded the rate of cyclisation but to a lesser extent. Conversions for the control ligand (**54a**) and the 5-methyl substituted ligand (**54b**) were of similar magnitude with the inductively donating (**54b**) the most efficient. In order to obtain more accurate rate data reactions mediated by ligands (**54b-d**) were then run individually against the control ligand (**54a**). A plot of  $\ln([sub]_0/[sub]_t)$  against time for each ligand produced the results shown in figures 4-6. The results obtained for the 5-nitro substituted ligand (**54c**) confirmed the striking reduction in rate previously observed (table 6). The reaction was stopped after 45 hours having proceeded only to give a 77:23 ratio of (**67**):(**68**). Assuming a *pseudo* first order rate plot where  $[cat]=constant$  and thus  $k = k(rds) \times k[cat]$ , this translates to a reaction rate of  $k[ATRC] = 2.3 \times 10^{-6} s^{-1}$  compared to that of  $k[ATRC] = 1.2 \times 10^{-4} s^{-1}$  for the control ligand (**54a**) (figure 4). The rates obtained for ligands (**54b,d**) were also consistent with initial observations. The use of the 5-methoxy ligand (**54d**) resulted in a decreased reaction rate of  $k[ATRC] = 9.97 \times 10^{-5} s^{-1}$  (figure 5) while the electron donating (**54b**) was found to be the most efficient with a reaction rate of  $k[ATRC] = 1.92 \times 10^{-4} s^{-1}$  (figure 6).

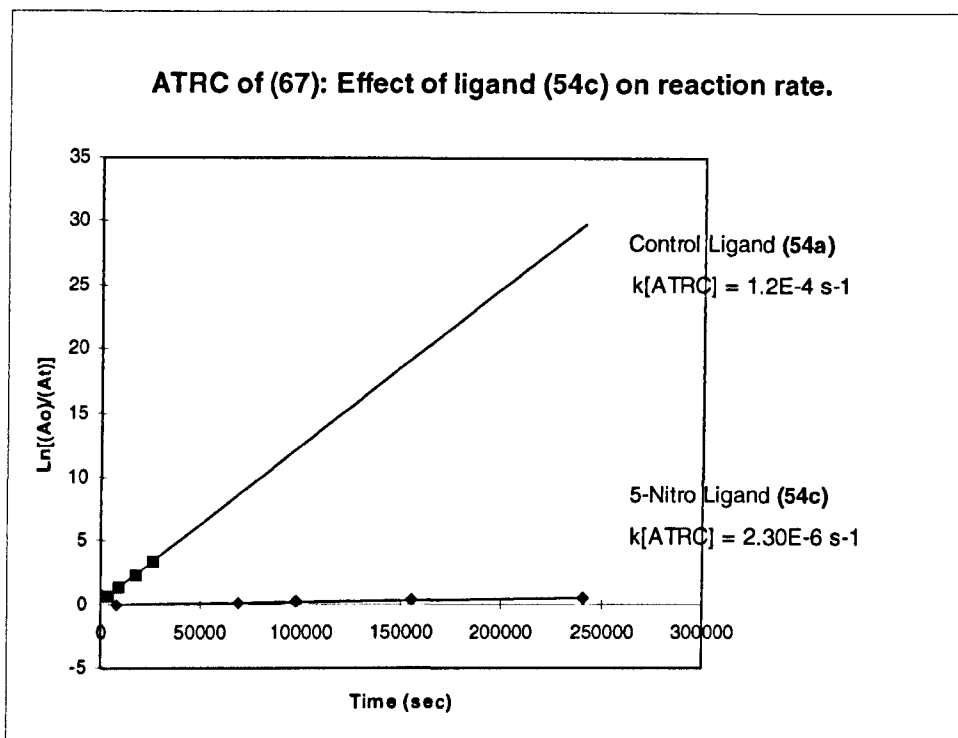


Figure 4. Rate of ATRC of (67) using ligand (54c).

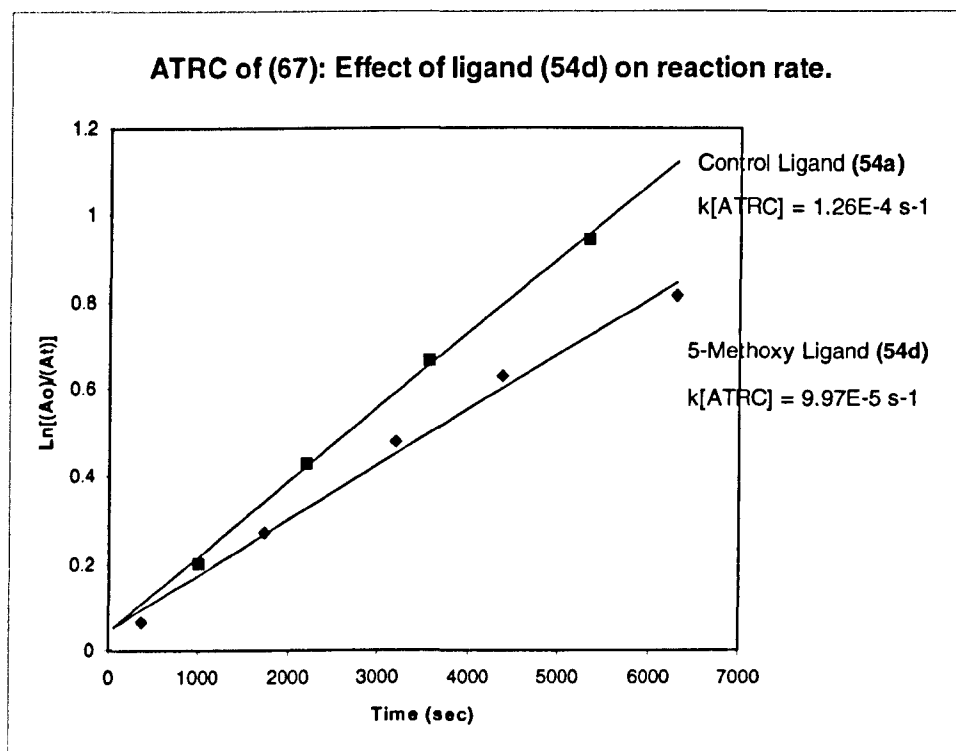
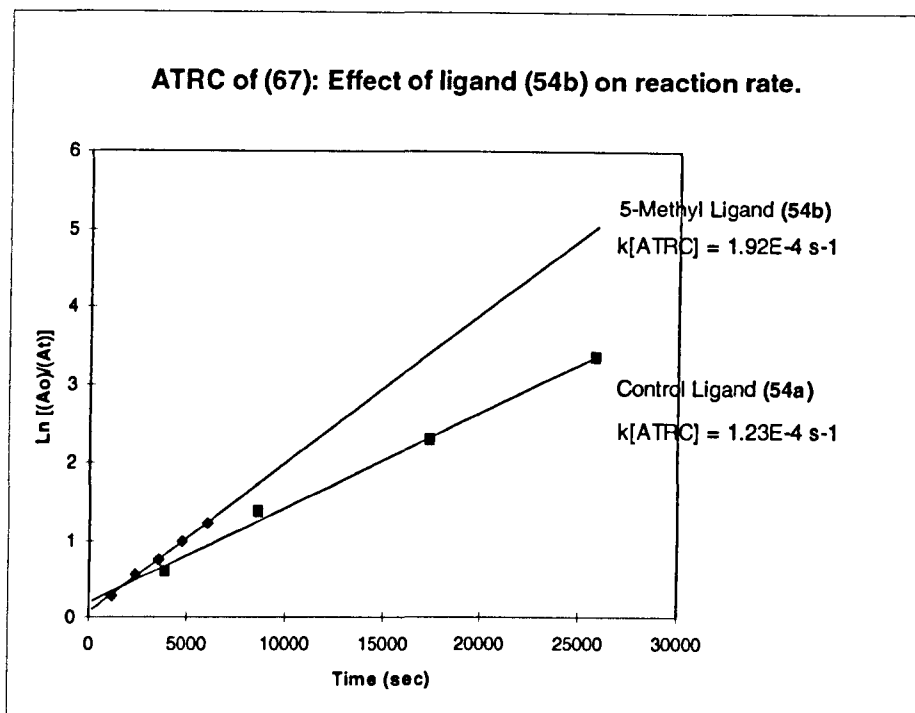


Figure 5. Rate of ATRC of (67) using ligand (54d).





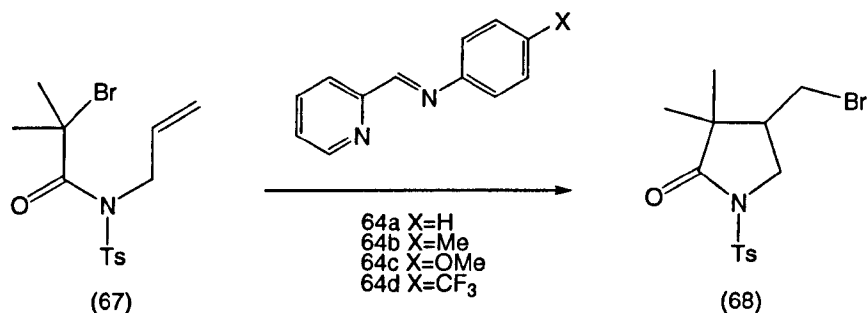
**Figure 6. Rate of ATRC of (67) using ligand (54b).**

These results demonstrate that in the ATRC of (67) the rate of reaction follows the order Me(54b)>H(54a)>OMe(54d)>NO<sub>2</sub>(54c). This implies that inductively increasing the electron density of the pyridine nitrogen increases the rate of ATRC reactions.

### 2.6.3 Copper mediated ATRC using *p*-substituted phenyl-pyridin-2-ylmethyleamine ligands (64a-d).

Next we investigated the affect of *p*-substituted phenyl-pyridin-2-ylmethyleamine ligands (64a-d). In this class of ligand the presence of a bulky phenyl group adjacent to the imine nitrogen might significantly retard cyclisation. However, aromatic substituents in the *para* position are in resonance with the imine nitrogen. Therefore, the relative rates

of reaction using ligands (**64a-d**) are of interest and will allow us to better assess the optimum electronic contributions of both nitrogen atoms to ATRC. Hence, reactions were conducted as before using (**67**) in dichloromethane (0.12 M) at room temperature with 30 mol% CuBr and 30 mol% of ligand (**64a-d**) (scheme 49).



**Scheme 49. Investigation of effect of ligands (64a-d).**

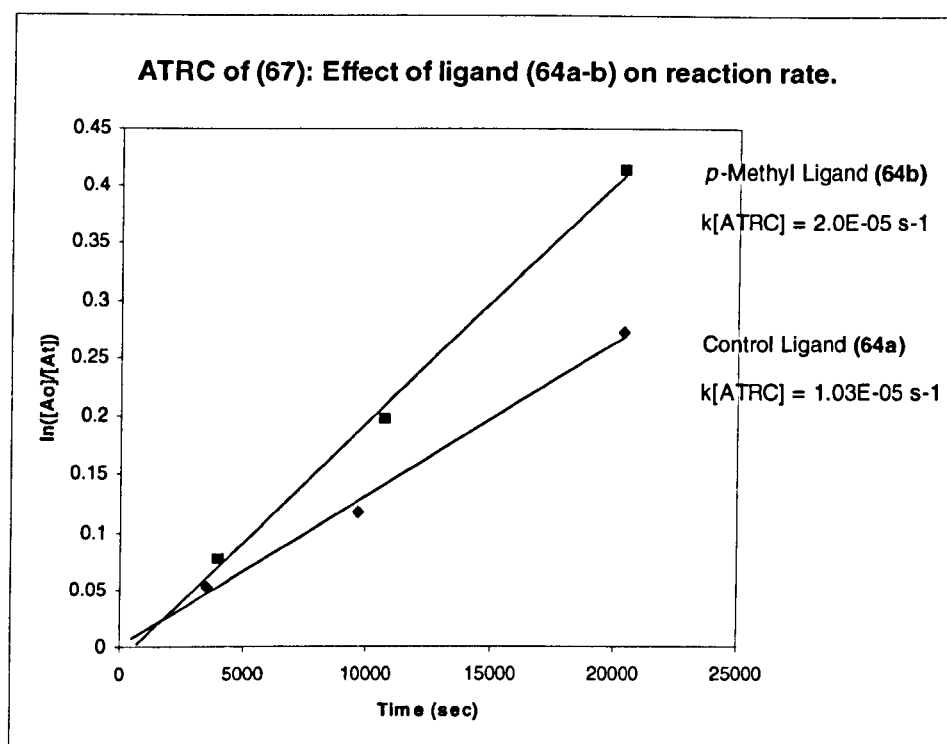
After 3 hours the reactions were worked up as previously described and the conversions determined from the crude <sup>1</sup>H NMR (table 7).

Ligand	Mass Balance (%)	Ratio 67:68
64a	97	26:74
64b	94	0:100
64c	96	87:13
64d	96	85:15

**Table 7. Cyclisation of 67: effect of ligand (64a-d) on conversion.**

The methoxy and CF<sub>3</sub> substituents (ligands **64c-d**) both impeded the cyclisation to a similar extent. Reaction using the control ligand (**64a**) proceeded to give a 26:74 ratio of

(67):(68) while the *p*-methyl ligand (64b) was again the most efficient (*cf.* section 2.6.2) having proceeded to completion after 3 hours. The rates of reaction for ligands (64a-b) were then determined (figure 7). As expected the results indicate that this class of ligand significantly retards cyclisation in comparison to the *N*-pentyl analogues (54a-d) (note that for 54a  $k[\text{ATRC}] = 2.23 \times 10^{-4} \text{ s}^{-1}$ ). This is probably due to steric reasons.

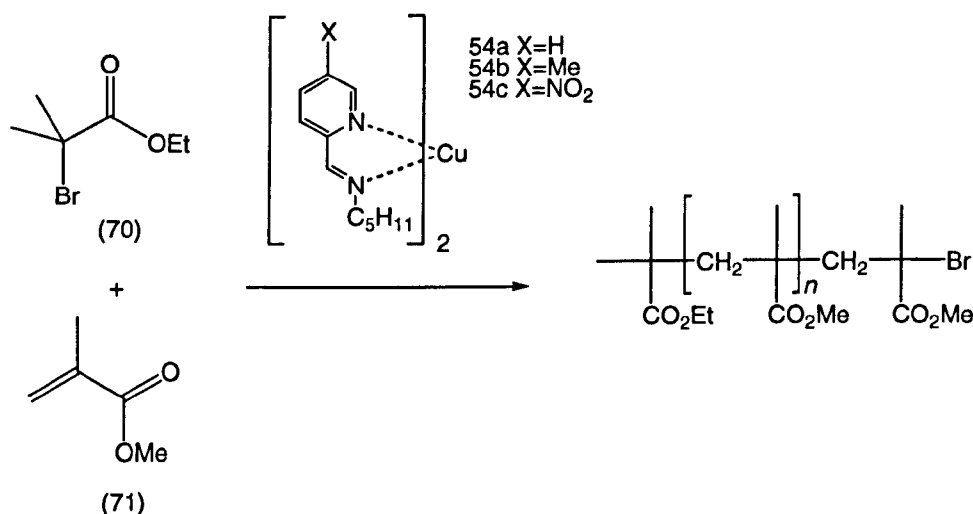


**Figure 7. Rate of ATRC of (67) using ligand (64a-b).**

The apparent lack of any pattern based on electronic considerations for the activity of the *p*-substituted phenyl-pyridin-2-ylmethyleneamine ligands (64a-d) suggests that these results are complicated further, perhaps by solubility arguments.

## 2.7 Atom transfer radical polymerisation reactions.

Atom transfer radical polymerisation (ATRP) has emerged as an efficient method for the polymerisation of vinyl monomers.<sup>18-21</sup> ATRP processes promoted by a range of low valent metal complexes including Cu(I)Br-bipyridine,<sup>19</sup> Ru(II)Cl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub><sup>20</sup> and Ni(II)[C<sub>6</sub>H<sub>3</sub>(CH<sub>2</sub>NMe<sub>2</sub>)<sub>2</sub>-2,6]Br<sup>21</sup> are known. More recent reports have demonstrated that *N*-pentyl-2-pyridylmethanimine (**54a**) copper(I) complexes are extremely effective for the ATRP of methyl methacrylate (MMA).<sup>12</sup> As a consequence we decided to examine the effectiveness of our modified NPMI ligands (**54a-c**) in the polymerisation of MMA. Polymerisation reactions were conducted by A. M. Heming of the Haddleton research group using ethyl 2-bromo-2-methylpropionate (**70**) as an initiator under standard living radical conditions (100:1:1:2 of [MMA]:[initiator]:[CuBr]:[**54a-c**] at 50% v/v in toluene at 90°C) (scheme 50).



Scheme 50. ATRP of MMA: Effect of ligands (**54a-c**).

Each reaction run exhibited a linear first-order rate plot indicating that the concentration of the propagating species remained constant throughout the reaction (figure 8).

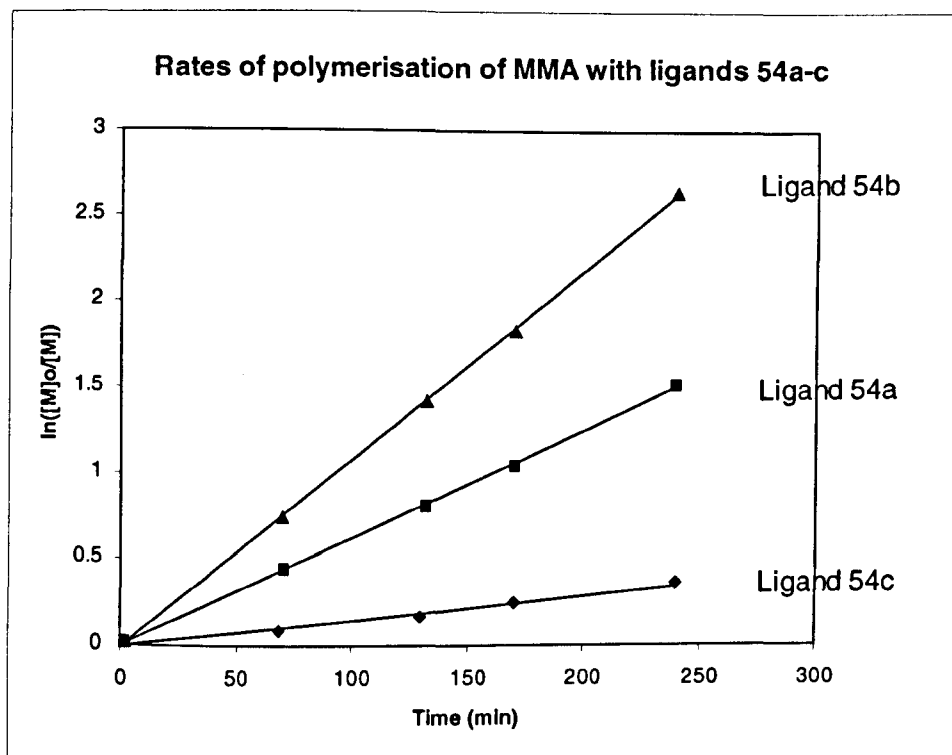


Figure 8. Rates of polymerisation of MMA with ligands (54a-c).

The rates of polymerisation of MMA parallel those found for the atom transfer cyclisation of (67) (section 2.6.2) with the electron withdrawing  $\text{NO}_2$  ligand (54c) showing poor activity, while the methyl substituted complex (54b) was more efficient than the control (54a).

The average molecular weights of polymers increased linearly with conversion in each case. Control was evidently greater when using ligands (54a-b) where  $M_n$ 's fit well with

those predicted. This was not the case for the reaction mediated by ligand (**54c**) which resembles a normal free radical polymerisation (figure 9).

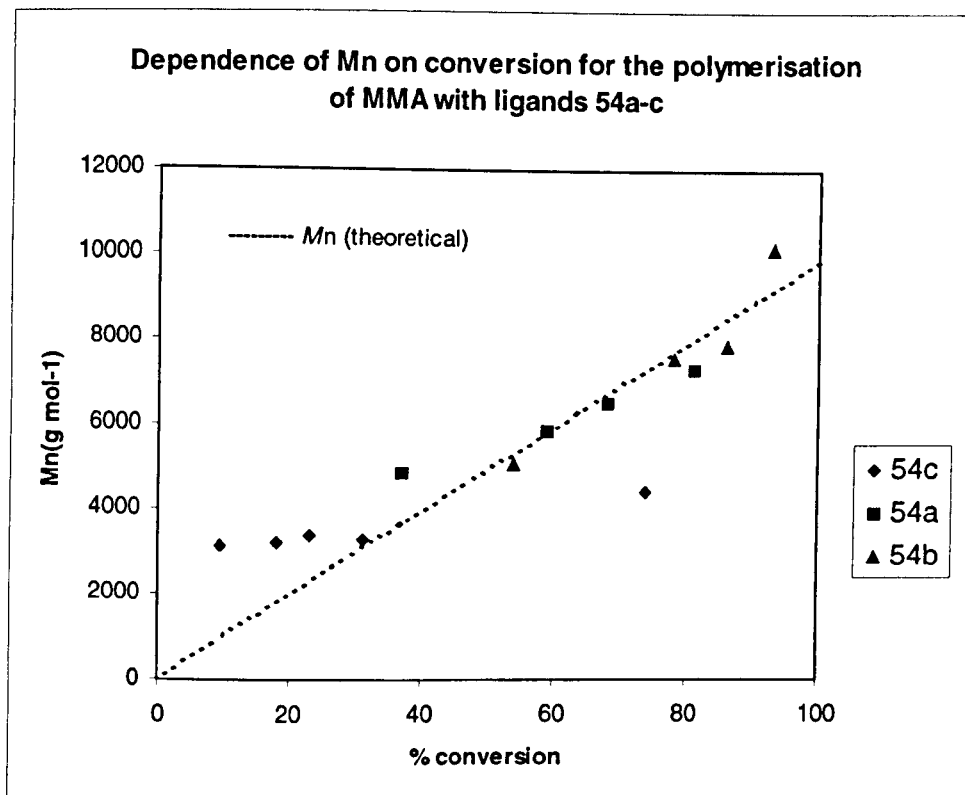


Figure 9. Dependence of  $M_n$  on conversion for ATRP of MMA with ligands 54a-c.

Polydispersities (PDIs) remained relatively low when using ligands (**54a-b**) indicating that initiation was fast compared to propagation and that all polymer chains increased at similar rates. However, the control in polydispersity with ligand (**54c**) was significantly poorer.

## 2.8 Conclusions.

We have demonstrated that substitution at the 6- and 5-position of the pyridine nucleus in *N*-pentyl-2-pyridylmethanimine ligands can effect the rate of both ATRC and ATRP reactions significantly. We have also shown that substitution at the imine nitrogen with *p*-substituted aromatic groups has a marked effect on the rate of ATRC. This may be due to electronic, steric or solubility reasons or a combination of all three.

Substitution at the 6-position (mesomerically linked to the pyridine nitrogen) caused the ATRC of the monobromo acetamide (**67**) to fail presumably due to steric effects. However, reaction with the activated trichloroacetamide substrate (**66**) indicated that the mesomerically electron donating methoxy ligand (**51c**) was more efficient than the 6-methyl ligand (**51b**). Groups at the 5-position can inductively alter the electron density of the pyridine nitrogen and mesomerically that of the imine nitrogen. Therefore, for each substituent a combination of both these effects will determine the overall rate of reaction. If the inductive effect on the pyridine nitrogen is the dominant feature then the order of activity would be expected to be Me(**54b**)>H(**54a**)>OMe(**54d**)>NO<sub>2</sub>(**54c**) thus following  $\sigma_m$ . However, if the electronic mesomeric effect of substituents onto the imine nitrogen is dominant the order would be expected to follow OMe(**54d**)>Me(**54b**)>H(**54a**)>NO<sub>2</sub>(**54c**) thus paralleling  $\sigma_p$ . Our results demonstrate that in the ATRC of (**67**) the rate of reaction follows the order (**54b**)>(**54a**)>(**54d**)>(**54c**) which suggests that inductive effects onto the pyridine nitrogen are the dominant feature for this class of ligand in cyclisation reactions. The rates of ATRC and ATRP reactions may therefore parallel the basicity of the pyridine nucleus. This would be consistent with the observation that more basic *sp*<sup>3</sup>

amine ligands (TMEDA, *N,N,N',N',N'*-pentamethyldiethylenetriamine and tris(*N,N*-dimethylaminoethylene)-amine) are more active catalysts for both ATRC<sup>22</sup> of (**67**) and ATRP of MMA.<sup>23</sup> Reaction with the most inductively electron withdrawing group (ligand **54c**) caused a striking decrease in the rate of both ATRC and ATRP. This may be due to the electronic effects discussed above however, the possibility of the NO<sub>2</sub> group competitively complexing the metal and changing the nature of the catalyst cannot be ruled out at this time. The apparent lack of any electronic pattern for the activity of the *p*-substituted phenyl-pyridin-2-ylmethylene-amine ligands (**64a-d**) suggests that the picture is more complicated, perhaps due to solubility reasons. Overall, the use of the modified NPMI ligands does not appear to result in a significant increase in rate compared to the control ligand (**54a**) (i.e. 100 times). Therefore, the effort required in their preparation is unlikely to warrant the use of these new ligands.

## 2.9 Future work.

The preparation and study of NPMI ligands substituted at the 4-position of the pyridine nucleus would allow us to test the conclusions presented here and provide a complete assessment of substituent electronic effects on rates of ATRC and ATRP. However, the synthesis of 4-substituted pyridine carboxaldehydes is not trivial and would entail considerable synthetic effort.



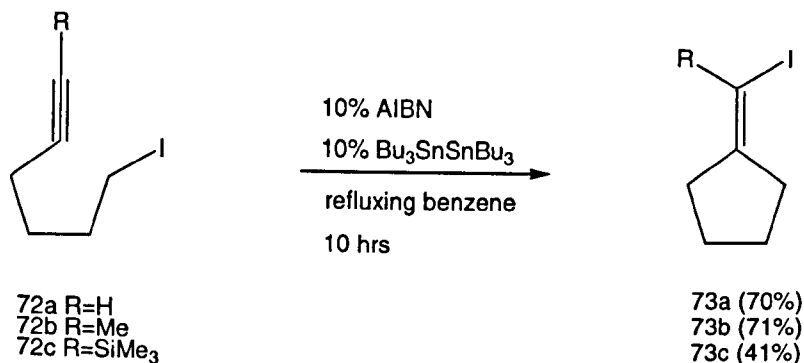
## **Chapter 3**

### **5-*Exo* Atom Transfer Cyclisation Onto Alkynes Mediated By Copper(I) Complexes**

#### **3.1 Introduction.**

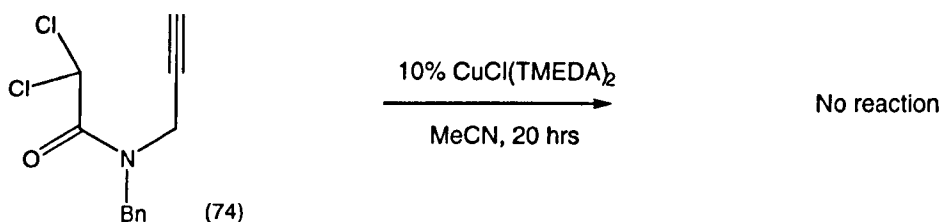
The use of radical cyclisation protocols for the preparation of cyclic systems continues to gain in importance.<sup>25</sup> However, while Bu<sub>3</sub>SnH-mediated cyclisations onto alkenes are generally facile, cyclisations onto terminal alkyne functional groups using organostannane methods can be complicated by competing hydrostannation.<sup>26</sup> In addition, these procedures are terminated under reductive conditions. However, functionality can be retained in products if cyclisations are carried out under atom transfer conditions. The use of (Bu<sub>3</sub>Sn)<sub>2</sub> to promote atom transfer cyclisations onto alkynes has been reported by Curran.<sup>27-28</sup> Thus, cyclisation of simple hex-5-ynyl iodides (**72**) with (Bu<sub>3</sub>Sn)<sub>2</sub> (10%) in refluxing benzene for 10 hours resulted in formation of vinyl iodides (**73**) in good yields (41-71%) (scheme 51).<sup>27</sup> This approach has also been successfully utilised by Curran in tandem radical cyclisations to give triquinanes.<sup>28</sup> However, due to the high toxicity of tin reagents a range of alternative atom transfer

catalysts have been developed including copper halide complexes of bipyridine,<sup>4</sup> *N*-alkylpyridylimines<sup>10,29</sup> and multidentate amines.<sup>6,30</sup>



**Scheme 51. Atom transfer cyclisation of hex-5-ynyl iodides.**

While these copper(I) based systems are known to mediate the atom transfer radical cyclisation of a range of haloacetamides onto alkene functional groups, there are very few reports on the application of this methodology to cyclisation onto alkynes.<sup>31</sup> Ghelfi has recently reported that attempted cyclisation of *N*-Benzyl-2,2-dichloro-*N*-prop-2-ynyl-acetamide (**74**) using CuCl(TMEDA)<sub>2</sub> failed (scheme 52),<sup>32</sup> although no explanation of why the reaction failed was given.



**Scheme 52. Attempted cyclisation of 1-dichloro-*N*-propargylacetamide (**74**)**

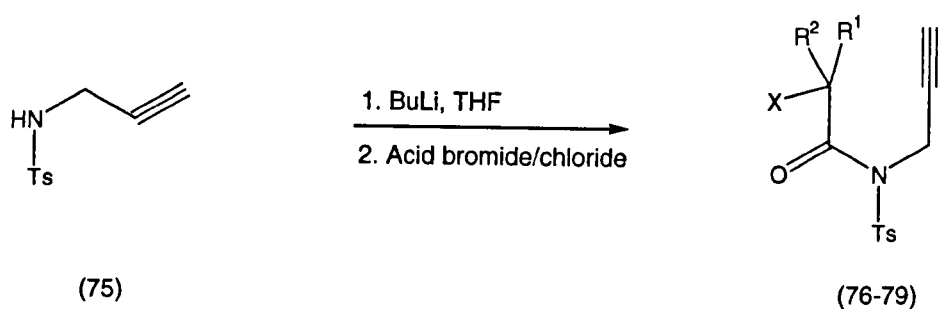
In the last chapter we demonstrated that copper halide *N*-alkyl-pyridylmethanimine complexes were effective in facilitating the atom transfer cyclisation of both activated and non-activated  $\alpha$ -haloacetamides onto alkenes. Consequently we propose to investigate the use of this system for cyclisation onto alkyne functional groups.

### 3.2 Precursor synthesis.

In 5-*exo* ATRC of haloacetamides onto alkenes the nature of the *N*-substituent often affects the efficiency of the cyclisations. Nagashima *et al.*<sup>33</sup> reported that efficiencies were greatest when tosyl or Boc substituents were used as the *N*-protecting group. Therefore, in addition to the *N*-benzyl precursor (**74**) used by Ghelfi, we prepared a range of *N*-tosyl and *N*-Boc cyclisation precursors in order to investigate their ATRC reactions onto alkynes.

#### 3.2.1 Synthesis of *N*-tosyl-mono, di and trihalo-*N*-propargylacetamides.

The general procedure for the preparation of the initially chosen *N*-tosyl cyclisation precursors (**76-79**) was carried out according to standard literature procedures. Thus, a solution of BuLi (1.6M in hexanes) was added dropwise over a period of 5 minutes to a stirred solution of *N*-propargyl-toluene-4-sulfonamide (**75**) (previously prepared by standard literature procedure) in dry THF at -78°C under nitrogen. The mixture was stirred for 30 minutes at this temperature, the appropriate acid halide was then introduced and the mixture stirred for a further 3 hours (scheme 53).



**Scheme 53. Synthesis of *N*-tosyl cyclisation precursors.**

The reaction was quenched by the careful addition of water. Then, following work-up, the crude compounds were purified by column chromatography to furnish the desired cyclisation precursors in moderate to good yield (table 8).

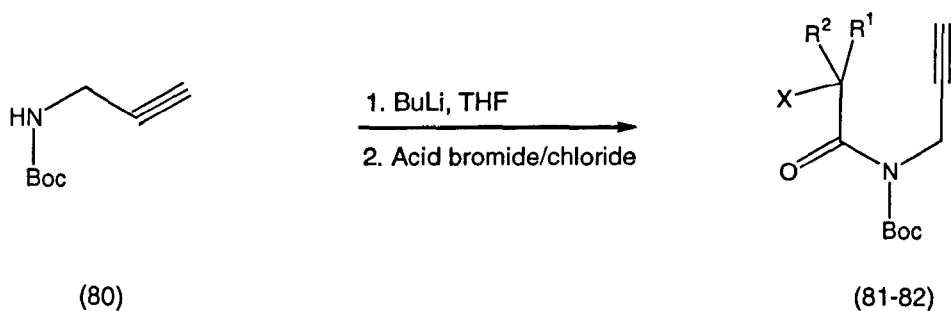
Precursor	R <sup>1</sup>	R <sup>2</sup>	X	Yield (%)
76	Me	Me	Br	55
77	Me	H	Br	65
78	Me	Cl	Cl	58
79	Cl	Cl	Cl	64

**Table 8. Yields of *N*-tosyl cyclisation precursors.**

The acid halide used for precursor (78) was not available commercially and was prepared from the corresponding acid by reaction with refluxing oxalyl chloride in accordance with standard literature procedure.

### 3.2.2 Synthesis of *N*-Boc-mono and dihalo-*N*-propargylacetamides.

The synthesis of the related *N*-Boc cyclisation precursors (**81-82**) was conducted in a manner similar to that used for the preparation of the *N*-tosyl derivatives described in section 3.2.1. Thus, BuLi (1.6M in hexanes) was added to a stirred solution of prop-2-ynyl-carbamic acid *tert*-butyl ester (**80**) in THF at -78°C. Addition of the appropriate acid halide and subsequent purification by flash column chromatography afforded precursors (**81-82**) in moderate yield (scheme 54).



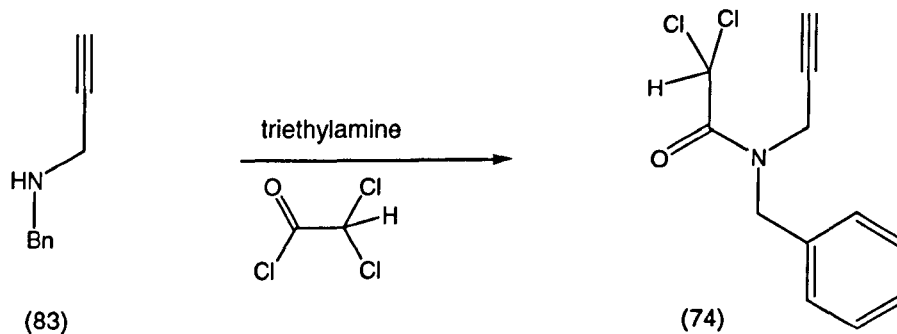
Precursor	R <sup>1</sup>	R <sup>2</sup>	X	Yield (%)
81	Me	Me	Br	76
82	Me	Cl	Cl	24

**Scheme 54. Synthesis of *N*-Boc cyclisation precursors.**

### 3.2.3 Synthesis of *N*-benzyl-2,2-dichloro-*N*-prop-2-ynyl-acetamide (**74**).

We also decided to re-examine the failed cyclisation reported by Ghelfi<sup>32</sup> of the *N*-benzyl precursor (**74**). Preparation of this precursor was conducted according to standard

literature procedures. Thus, to a solution of benzyl-prop-2-ynyl-amine (**83**) (previously prepared by literature procedure) and triethylamine in dichloromethane was added dichloroacetyl chloride dropwise. The mixture was stirred for 4 hours at room temperature and then was added, with stirring, to a saturated aqueous solution of potassium carbonate. The mixture was extracted with ether and the combined extracts were then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography furnished *N*-benzyl-2,2,dichloro-*N*-prop-2-ynyl-acetamide (**74**) in 62% yield (scheme 55).



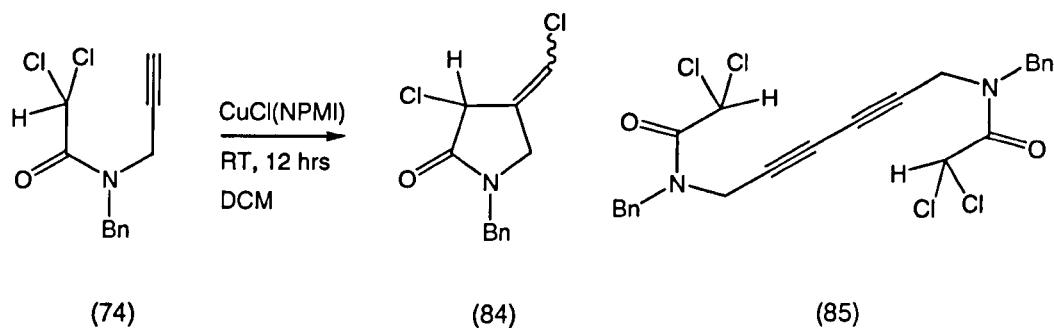
**Scheme 55. Preparation of *N*-benzyl-2,2,dichloro-*N*-prop-2-ynyl-acetamide.**

The N.M.R spectra of the *N*-benzyl protected precursor (**74**) exhibited splitting of individual signals. The precursor was isolated as an inseparable 1:1 mixture of rotomers, which is consistent with previously published results.<sup>32</sup>

### 3.3 Cyclisation reactions.

#### 3.3.1 Cyclisation of dichloro-*N*-propargylacetamides.

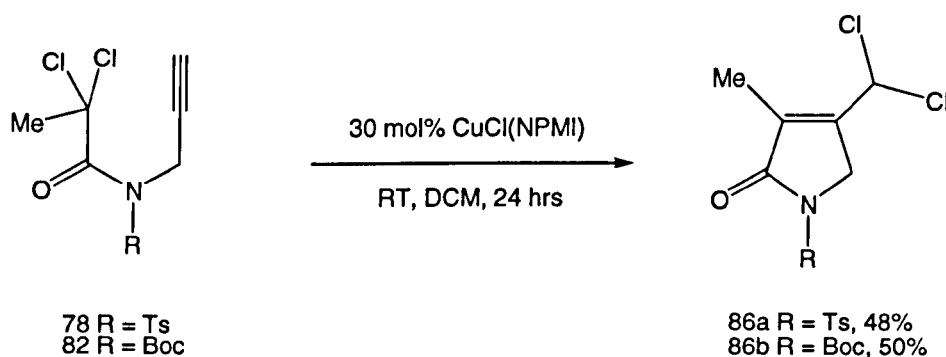
Attempted cyclisation of the *N*-benzyl substituted precursor (74) with 30 mol% CuCl(NPMI) failed with only starting material being recovered. We therefore repeated the reaction using an increased amount of catalyst. Thus, to a 0.12M solution of *N*-benzyl-2,2,dichloro-*N*-prop-2-ynyl-acetamide (74) in dry dichloromethane under nitrogen was added CuCl (1 equivalent) and *N*-pentyl-2-pyridylmethanimine (NPMI) (1 equivalent). The resulting mixture was stirred at room temperature overnight. The crude mixture was then passed through a short silica plug eluting with dichloromethane. Interestingly, the reaction furnished not the desired atom transfer product (84), but gave the dimer (85) exclusively in 98% yield (scheme 56).



Scheme 56. Dimerisation of *N*-benzyl-2,2,dichloro-*N*-prop-2-ynyl-acetamide.

Terminal alkynes are known to undergo facile oxidative dimerisation and intermolecular coupling reactions when subjected to copper halide pyridine/amine complexes.<sup>34</sup> Therefore formation of the dimer (**85**) may also account for the failed cyclisation of (**74**) originally reported by Ghelfi.<sup>32</sup>

Next we turned our attention to the cyclisation of the related *N*-tosyl and *N*-Boc protected dichloro-*N*-propargylacetamides (**78**, **82**). We were pleased to find that these precursors underwent cyclisation in the presence of 30 mol% CuCl(NPMI) at room temperature in dichloromethane to furnish the corresponding atom transfer products (**86a-b**) (scheme 57).



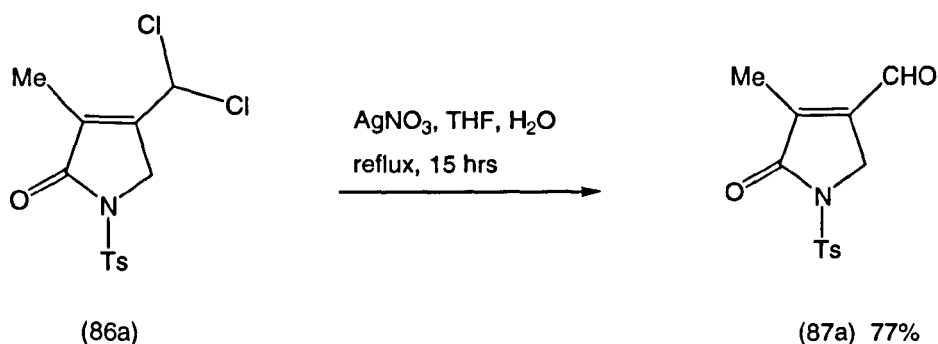
**Scheme 57. ATRC of *N*-Boc and *N*-tosyl dichloro-*N*-propargylacetamides.**

No dimerisation products were detected. However, the reactions did not go to completion and gave a 1:1 mixture of cyclised product:starting material after 24 hrs at room temperature (100% mass balance). Extended reaction times did not significantly improve



upon this yield. However, stirring (**78**) with 1 equivalent of CuCl(NPMI) afforded an 8:1 ratio of (**86a**):(**78**) (89% yield).

The *gem* dihalide (**86a**) was readily converted to the corresponding aldehyde derivative (**87a**) by reaction with aqueous silver nitrate in refluxing THF (scheme 58). This reaction provides a useful functional group for further synthetic manipulation and demonstrates the significance of retaining functionality in products under atom transfer conditions.

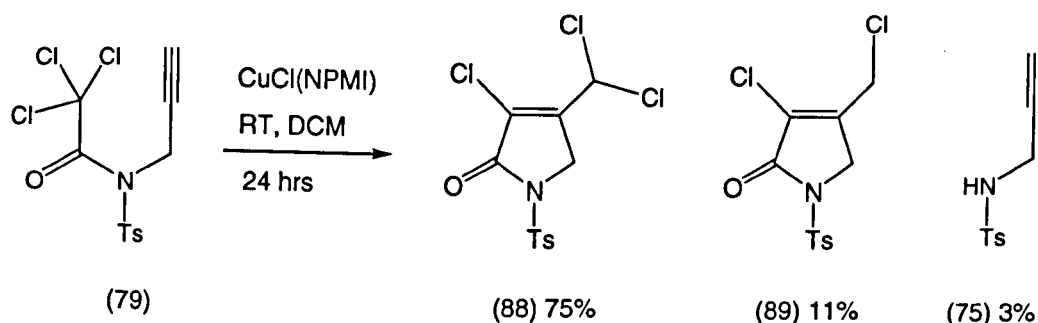


**Scheme 58. Conversion of *gem* dihalide (**86a**) to aldehyde (**87a**).**

### 3.3.2 Cyclisation of 4-methyl-*N*-prop-2-ynyl-*N*-(2,2,2-trichloroacetyl)-benzene sulfonamide.

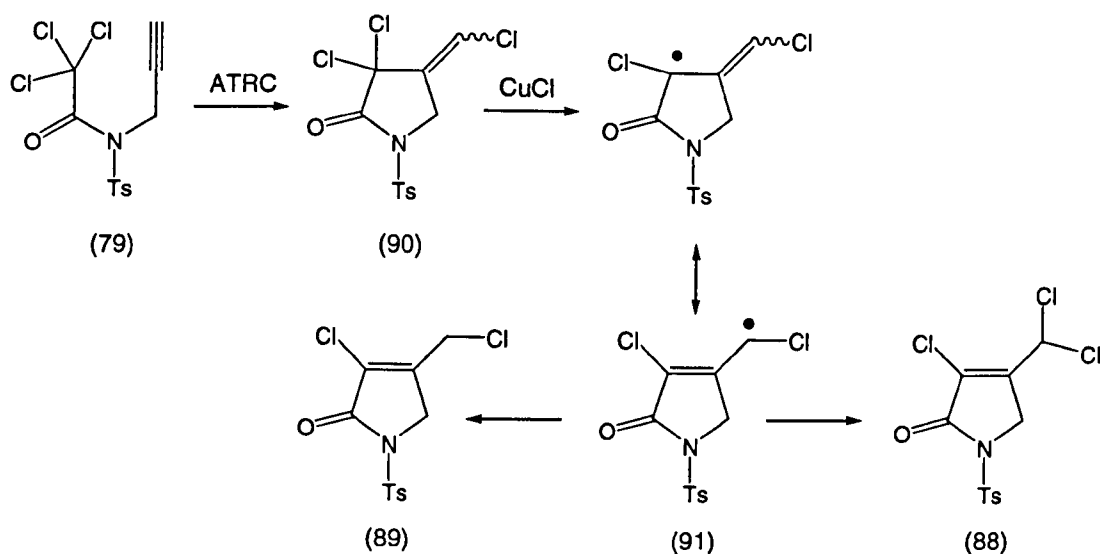
Having initially focussed on the reactions of dichloroacetamides (**74**, **78**, **82**) we next attempted cyclisation of the trichloroacetamide derivative (**79**). Cyclisation under standard conditions with 30 mol% CuCl(NPMI) gave a mixture of products in a mass

balance of 96% after 24 hrs. Following purification by column chromatography the mixture was found to consist of cyclised products **(88)** (75%) and **(89)** (11%), the cleaved *N*-tosyl amide **(75)** (3%) and a small amount of unreacted starting material **(79)** (11%) (scheme 59).



**Scheme 59. Cyclisation of trichloroacetamide (79).**

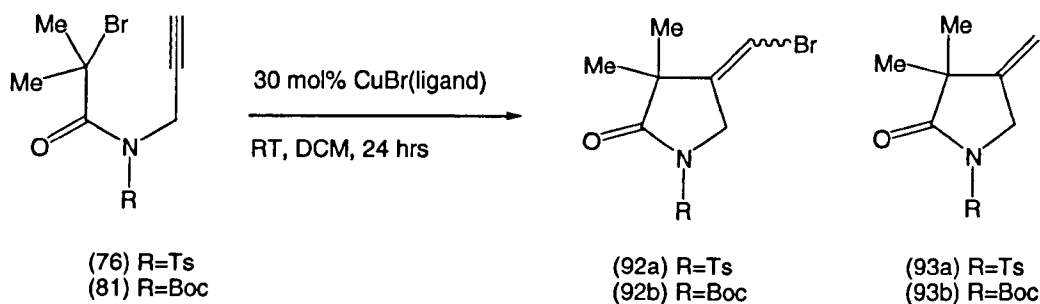
The formation of the two major products **(88)** and **(89)** can be rationalised by initial atom transfer cyclisation of **(79)** to give vinyl chloride **(90)** followed by abstraction of a second halogen atom to furnish the allyl radical **(91)** (scheme 60). Radical species **(91)** may then undergo a second atom transfer reaction resulting in the observed product **(88)**. Alternatively, reduction of **(91)** (either from the solvent or *via* the ligand) would give rise to the minor cyclic product **(89)**. A secondary halogen atom abstraction would also account for the  $\alpha,\beta$ -unsaturated  $\gamma$ -lactam products **(86a-b)** obtained from the cyclisation of dichloroacetamides **(78, 82)** (section 3.3.1). Although, in the case of the dichloroacetamide precursors, reactions were cleaner providing only one cyclised product and no products arising from reduction of the intermediate allyl radical were detected.



**Scheme 60. Proposed mechanism of formation of cyclised products (88) and (89).**

### 3.3.3 Cyclisation of monobromo-*N*-propargylacetamides.

Following the successful atom transfer cyclisation of di- and trihaloacetamides with CuCl(NPMI), we next investigated the cyclisation of the less activated monobromoacetamide precursors (**76-77**, **81**). Cyclisation of (**76**) with 30 mol% CuBr(NPMI) in dichloromethane at room temperature for 24 hours furnished two products, the atom transfer product (**92a**) (2:5 mixture of (*E*)- and (*Z*)- isomers) as well as the reduced product (**93a**) (scheme 61). Thus, it may be inferred that the intermediate vinyl radical can undergo either bromine atom transfer to produce (**92a**) or hydrogen atom transfer to give (**93a**).



Scheme 61. Cyclisation of monobromoacetamides (76, 81).

As a consequence we were able to significantly alter the ratio of products (92) and (93) by conducting the reaction with different solvents or ligand (table 9).

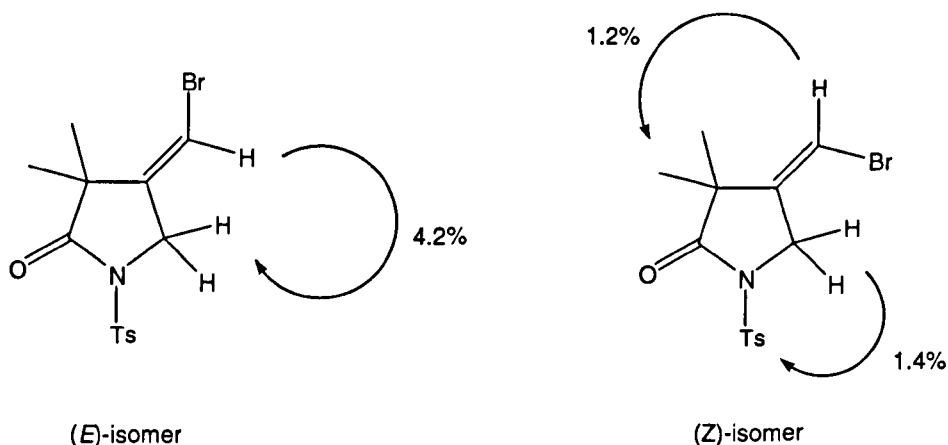
Substrate	Ligand	Solvent	92:93	92 ( <i>E:Z</i> )
76	NPMI	DCM	25:1 (96)	2:5
76	NPMI	Benzene	74:1 (94)	1:4
76	Tren-Me <sub>6</sub>	THF	1:20 (95)	1:4
81	NPMI	DCM	10:1 (96)	1:2

Percentage yield of combined products shown in brackets.

Table 9. Ratio of atom transfer products: Effect of solvent and ligand.

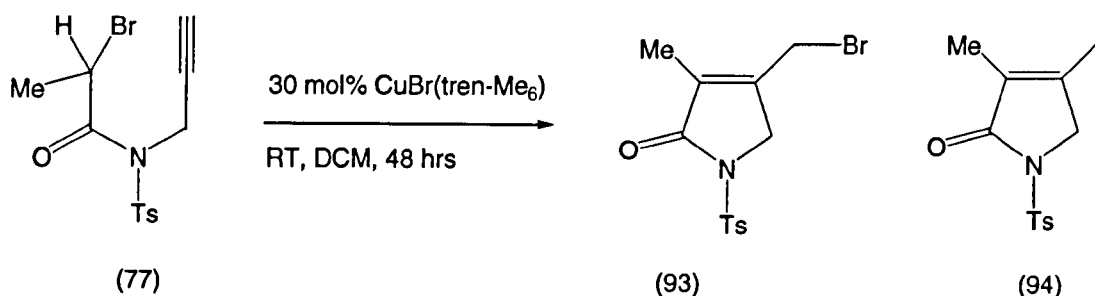
Thus, repeating the reaction in benzene gave the bromine atom transfer product (92) almost exclusively. This is presumably due to the poorer hydrogen atom donating ability of benzene compared to dichloromethane. Conversely, the use of a better hydrogen atom donor (THF) in conjunction with the tren-Me<sub>6</sub> ligand leads to (93) as the major product.

Independent of reaction conditions (table 9), the bromine atom transfer product (**92**) was obtained as a separable mixture of (*E*)- and (*Z*)- isomers. The major isomer was confirmed as (*Z*)-4-bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one by n.O.e difference data, the percentage enhancements are shown in figure 10.



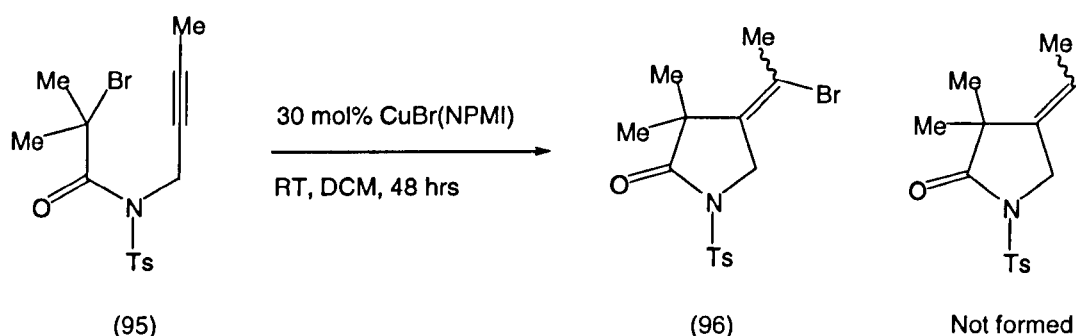
**Figure 10. n.O.e evidence for the major isomer of cyclised product (**92**).**

Next we investigated the reaction of the deactivated 2-bromo precursor (**77**). However, reaction with 30 mol% CuBr(NPMI) overnight at room temperature did not lead to any observed cyclisation product and only starting material was recovered. Repeating the reaction with the more activated CuBr(tren-Me<sub>6</sub>) catalyst system resulted in only 50% conversion after 48 hours at room temperature. The reaction gave a 1:1 mixture of the two products (**93**) and (**94**), which were subsequently isolated in 35% yield (scheme 62).



**Scheme 62. Cyclisation of deactivated monobromo precursor (77).**

Finally, having investigated the cyclisation of a range of haloacetamides onto terminal alkyne functional groups, we were interested in attempting cyclisation onto a disubstituted alkyne precursor. Thus, *N*-(2-bromo-2-methylpropionyl)-*N*-but-2-ynyl-4-methylbenzenesulfonamide (**95**) was prepared in 62% yield from *N*-but-2-ynyl-4-methylbenzenesulfonamide according to the procedure outlined in section 3.2.1. Interestingly, cyclisation of the disubstituted alkyne (**95**) with 30 mol% CuBr(NPMI) in dichloromethane at room temperature proceeded to give the bromine atom transfer product (**96**) only. (1:1 mixture of (*E*)- and (*Z*)- isomers in 94% yield) (scheme 63).



**Scheme 63. Cyclisation of disubstituted alkyne precursor (95).**

No products arising from hydrogen atom transfer were detected suggesting that the intermediate vinyl radical is less reactive towards hydrogen abstraction than those derived from the corresponding reactions of terminal alkynes (**76**) and (**81**) (scheme 61).

### 3.4 Conclusions.

We have demonstrated that a range of trichloro-, dichloro- and monobromo-acetamides may undergo CuX(NPMI) or CuX(tren-Me<sub>6</sub>) mediated 5-*exo* atom transfer radical cyclisations onto alkynes at room temperature. Cyclisation of trichloro-, dichloro- and 2-bromo-acetamides (**77-79**, **82**) resulted in formation of  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams in moderate to good yield. However, reaction of mono-bromoacetamides (**76**) and (**81**) proceeded to give exocyclic alkene derivatives which could be terminated reductively or by bromine atom transfer depending upon the nature of the ligand and solvent used. The nature of the *N*-substituent also affected the reaction. Thus, while *N*-tosyl and *N*-Boc protected precursors underwent atom transfer cyclisation, reaction of the *N*-benzyl substrate (**74**) resulted in exclusive formation of the dimer. No products arising from 6-*endo* cyclisation were observed for either the terminal or disubstituted alkynes. In general, the relatively slow rate of conversion (in comparison to their alkene counterparts) is not surprising and is often characteristic of cyclisation reactions onto alkynes.<sup>35</sup>

## Chapter 4

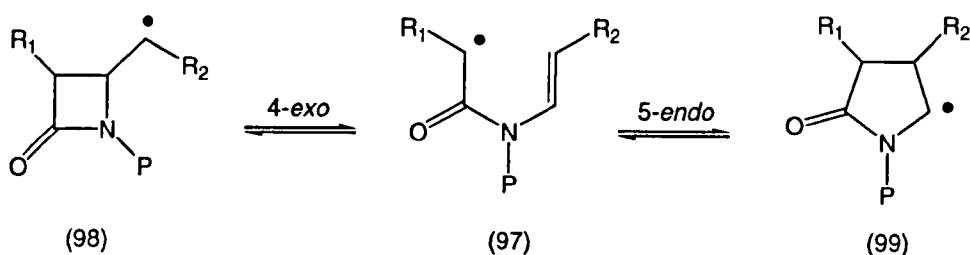
### Efficient $\beta$ -Lactam Synthesis Via 4-*Exo* Atom Transfer

#### Radical Cyclisation

##### 4.1 Introduction.

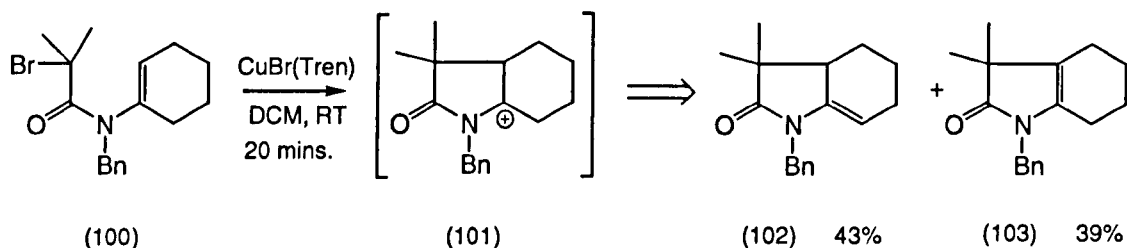
The use of cyclisation protocols to prepare  $\beta$ -lactam compounds continues to gain in importance.<sup>36</sup> Cyclisation using tin-based radical methods is possible<sup>37</sup> but suffers from a number of disadvantages including the toxicity of the reagent, and poor yields due to competitive trapping of non-cyclised radicals. Consequently, we wished to examine the use of copper-mediated atom transfer radical cyclisation (ATRC) for the preparation of  $\beta$ -lactams. While copper systems are known to mediate 5-*exo* ATRC of a range of haloacetamides there are very few reports on the application of this methodology to 4-*exo* versus 5-*endo* cyclisation onto enamides (scheme 64).<sup>38</sup> This is probably because 5-*endo* cyclisation is a disfavoured process<sup>39</sup> and 4-*exo* cyclisation is generally a reversible process in which the release of ring strain strongly biases the equilibrium toward the direction of the acyclic radicals.<sup>40</sup>





**Scheme 64. 4-*Exo* versus 5-*endo* ring closure of halo-enamides.**

In these examples the cyclisation of halo-enamides generally results in formation of the 5-*endo* derived product.<sup>41</sup> This is intriguing because the initial carbamoylmethyl radical (97) will preferentially form  $\gamma$ -lactam (99) (via 5-*endo* ring closure) rather than undergo the more favourable 4-*exo* cyclisation leading to  $\beta$ -lactam (98). The Clark group<sup>42</sup> has demonstrated this preference for the 5-*endo* mode of cyclisation. Thus, reaction of tertiary bromo-enamide (100) (scheme 65) with 30 mol% CuBr(Tren-Me<sub>6</sub>) was observed to furnish the unsaturated pyrrolidine derivatives (102-103) in excellent yield. No  $\beta$ -lactams were isolated from these reactions and products were proposed to arise not from atom transfer but from pathways involving an intermediate *N*-acyl iminium ion (101).

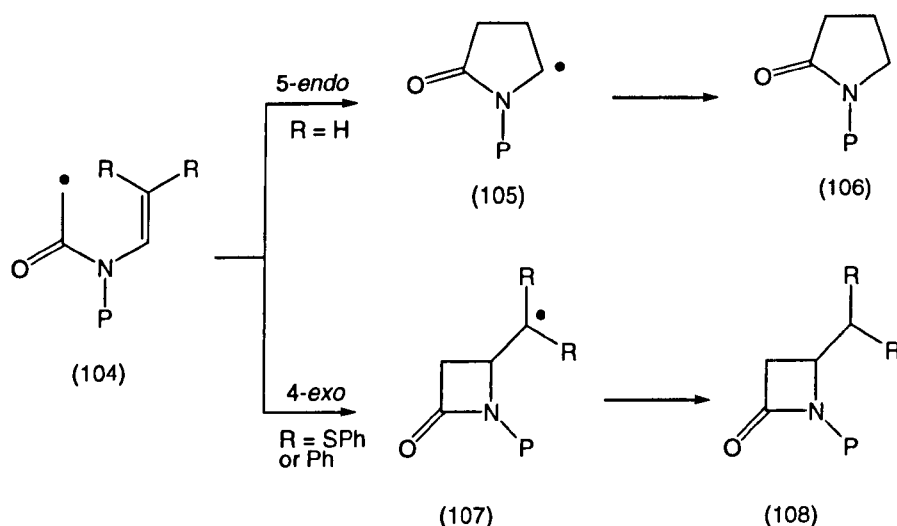


**Scheme 65. Oxidative 5-*endo* cyclisation of enamide (100).**

However, the regioselectivity of 4-*exo* versus 5-*endo* radical cyclisations might be influenced by the nature of the substituents, both at the radical centre and at the terminal end of the alkene. Hence, suitably designed precursors might be used to encourage 4-*exo* radical cyclisation leading to  $\beta$ -lactam formation.

#### 4.1.1 Substituent effects on the 4-*exo* versus 5-*endo* pathway.

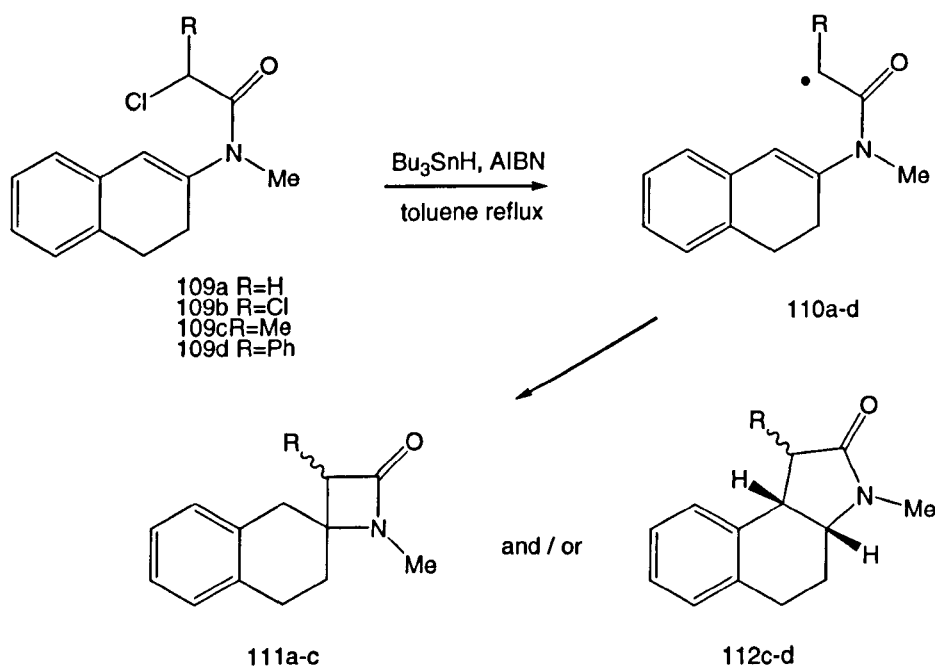
Substituents on the enamide double bond play a crucial role in determining the regiochemistry of cyclisations that proceed via a 4-*exo* or 5-*endo* pathway. The 4-*exo* mode of ring closure is generally only observed when bulky radical stabilising groups are introduced on the  $\beta$ -position of the double bond. Thus, it has been reported that  $\text{Bu}_3\text{SnH}$  mediated cyclisation of enamide (104) results in formation of  $\beta$ -lactam (108) when  $\text{R} = \text{PhS}$  or  $\text{Ph}$  (scheme 66).<sup>43</sup>



Scheme 66. Effect of groups at the  $\beta$ -position of the enamide double bond.

These groups serve to stabilise the  $\beta$ -lactam radical (**107**) by electronic effects and also sterically hinder attack at the  $\beta$ -position of carbamoyl radical (**104**).

Substituents at the radical centre also affect the regiochemistry of 4-*exo* versus 5-*endo* cyclisations. Ikeda<sup>44</sup> has reported that  $\text{Bu}_3\text{SnH}$  mediated radical cyclisation of 2-chloro-*N*-(3,4-dihydro-2-naphthyl)-*N*-methylacetamides (**109a-d**) in boiling toluene gave  $\beta$ -lactams (**111a-c**) and/or  $\gamma$ -lactams (**112c-d**) depending on the nature of the substituent at the carbamoylmethyl radical centre (**110a-d**) (scheme 67).



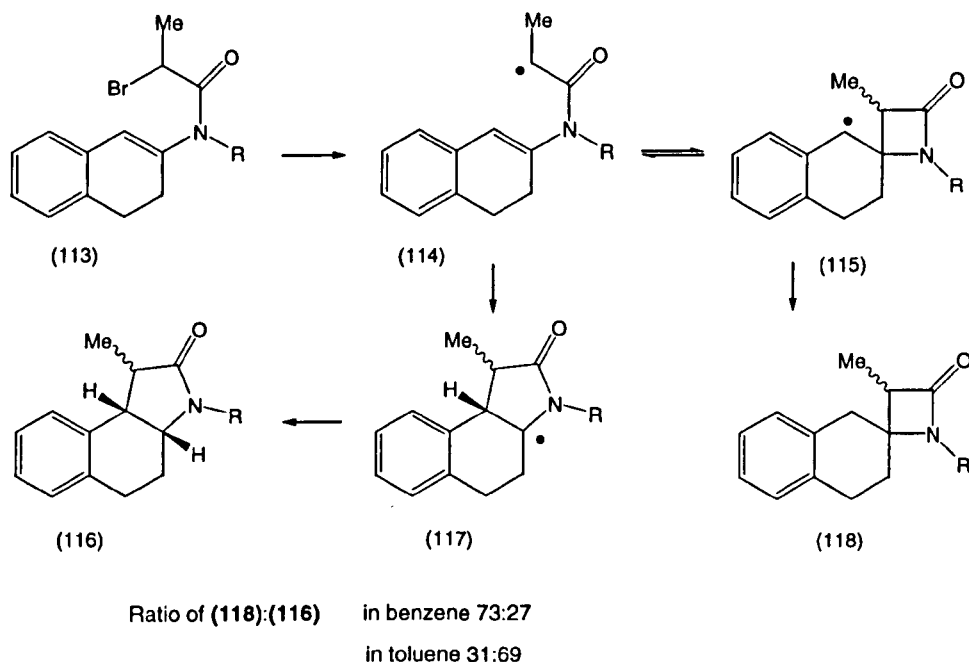
**Scheme 67.** The effect of substituents at the radical centre upon regiochemistry.

These results<sup>44</sup> indicate that  $\beta$ -lactam formation is favoured when R=H or Cl (scheme 67), while radical stabilising substituents such as methyl, phenyl, phenylthio, dimethyl

and dichloro lead predominantly or exclusively to  $\gamma$ -lactam formation.

#### 4.1.2 4-*Exo* versus 5-*endo* cyclisation mechanism.

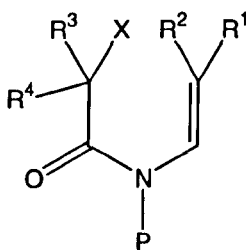
The observations outlined in the last section may be rationalised on the basis of a reversible cyclisation mechanism in which the  $\beta$ -lactam is the kinetic product and the  $\gamma$ -lactam is the thermodynamic product. Support for this proposed mechanism has been derived from the examination of the effects of reaction temperature.<sup>45</sup> Thus, 2-bromopropanamide (**113**) when treated with  $\text{Bu}_3\text{SnH}$  in boiling benzene (at  $80^\circ\text{C}$ ) gave  $\beta$ -lactam (**118**) as the major product, whereas in boiling toluene (at  $110^\circ\text{C}$ ) the  $\gamma$ -lactam (**116**) was obtained as the major product (scheme 68).



**Scheme 68.** Effect of temperature on mode of cyclisation.

Hence, at higher temperatures (boiling toluene) the ring opening of radical (**115**) occurs rapidly and the resulting radical (**114**) will cyclise in a 5-*endo* manner to give the thermodynamically stable (**117**). However, at lower temperatures (boiling benzene) the kinetically favoured 4-*exo* cyclisation predominates.

Consequently, in order to promote  $\beta$ -lactam formation, we were interested in investigating the copper-mediated ATRC of enamides that were substituted at the terminal end of the alkene only (scheme 69).

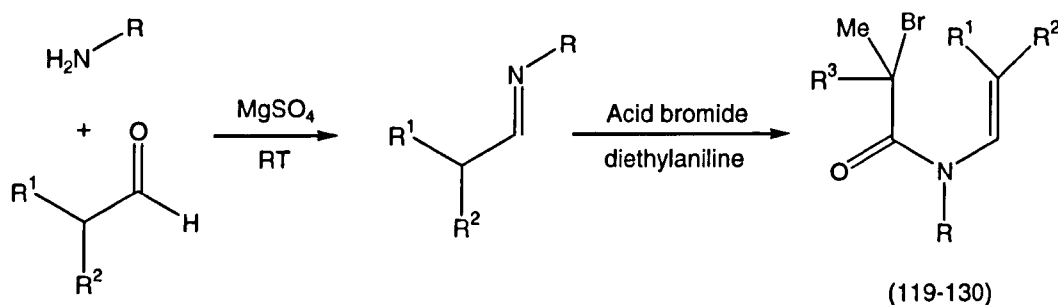


**Scheme 69. General structure of terminally substituted enamide precursors.**

By using precursors of this type we hoped to impede the rate of any competing 5-*endo* cyclisation and stabilise the resulting  $\beta$ -lactam radical. In addition, the use of a highly active atom transfer catalyst at relatively low temperature should facilitate rapid trapping to give the kinetic 4-*exo* product.

## 4.2 Precursor synthesis.

We prepared a range of enamide substrates in order to assess their suitability towards 4-*exo* radical cyclisation. The general procedure for the preparation of the initially chosen precursors (**119-130**) was carried out using standard literature procedures. Thus, the appropriate aldehyde (1.0 eq.) was added to a solution of the required primary amine and excess anhydrous magnesium sulfate in dichloromethane under an atmosphere of nitrogen. The mixture was stirred for four hours at room temperature then the magnesium sulfate was removed by filtration and the solvent removed under reduced pressure (scheme 70). To a solution of the resulting imine in dry dichloromethane was added the appropriate acid bromide followed by diethylaniline. The mixture was stirred for two hours at room temperature then washed with a 10% solution of HCl followed by a saturated solution of sodium chloride. The organic phase was then dried and concentrated under reduced pressure to yield the crude products.



**Scheme 70. Synthesis of bromo-enamides (119-130).**

The crude bromo-enamides required purification by column chromatography and the overall yields were generally good (28%-74%) (table 10). Using this method we prepared a range of different substrates in which the nature of the *N*-protecting group was varied from benzyl, *para*-methoxy benzyl and *o*-bromo benzyl as well as sterically (1°, 2° and 3° groups). We also investigated the effect of alkene substituents by enclosing them in 5-, 6- and 7-membered rings as well as using non-cyclic substituents. Finally we prepared substrates in which cyclisation would take place *via* a 3° and a 2° radical.

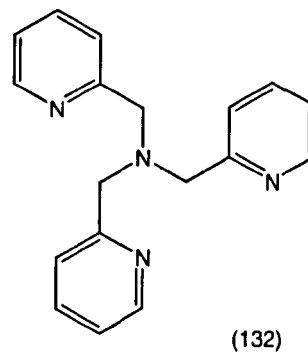
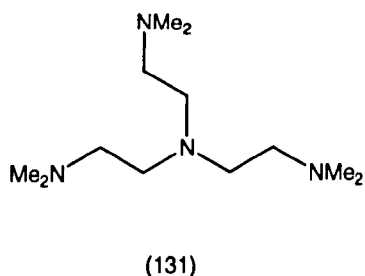
Precursor	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield
119	CH <sub>2</sub> Ph	(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>5</sub>	Me	58%
120	CH <sub>2</sub> Ph	(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>5</sub>	H	40%
121	CH <sub>2</sub> Ph	CH <sub>3</sub>	CH <sub>3</sub>	Me	74%
122	CH <sub>2</sub> Ph	(CH <sub>2</sub> ) <sub>4</sub>	(CH <sub>2</sub> ) <sub>4</sub>	Me	53%
123	CH <sub>2</sub> Ph	(CH <sub>2</sub> ) <sub>6</sub>	(CH <sub>2</sub> ) <sub>6</sub>	Me	63%
124	CH <sub>2</sub> Ph	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	Me	52%
125	CH <sub>2</sub> Ph	H	CHCH <sub>3</sub> CH <sub>3</sub>	Me	60%
126	PMB	(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>5</sub>	Me	55%
127	<i>t</i> -Bu	(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>5</sub>	Me	28%
128	<i>i</i> -Bu	(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>5</sub>	Me	47%
129	<i>o</i> -bromo Bn	(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>5</sub>	Me	66%
130	CHCH <sub>3</sub> Ph	(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>5</sub>	Me	58%

**Table 10. Yields of bromo-enamide cyclisation precursors (119-130).**

Not all the aldehydes required for the preparation of substrates were commercially available and those that were not were synthesised from their corresponding alcohols using pyridinium chlorochromate (PCC).<sup>46</sup>

### 4.3 Cyclisation reactions.

Initial studies (chapter 2) and other work recently reported within the group<sup>47</sup> has demonstrated that the nature of the ligand in copper(I) mediated atom transfer cyclisations has a dramatic effect upon the rate of reaction. Tertridentate ligands (**131-132**) were found to be the most active in simple 5-*exo* radical cyclisations allowing reactions to be carried out under milder conditions than existing copper-bipyridine<sup>48</sup>, copper-TMEDA<sup>49</sup> or  $\text{RuCl}_2(\text{PPh}_3)_3$ <sup>50</sup> technologies.

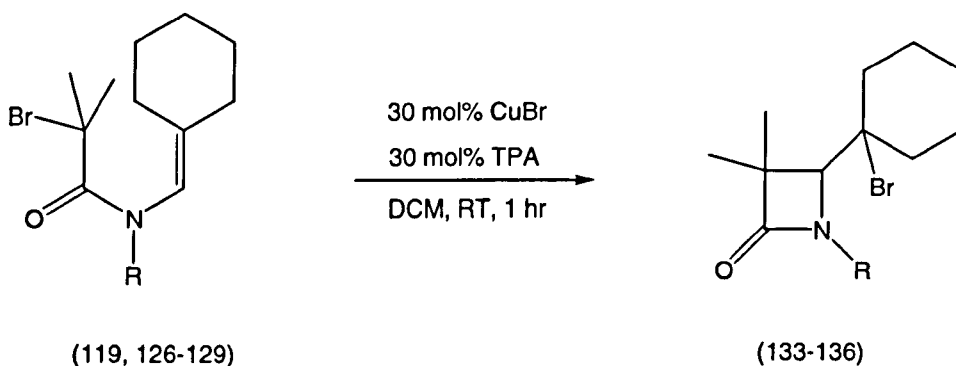


Therefore, tripyridylamine (TPA) ligand (**132**) was selected for use in the cyclisation of bromo-enamides (**119-130**). The extremely active nature of this catalyst should permit reactions to be conducted at room temperature or below with rapid trapping, therefore hopefully favoring formation of the kinetic 4-*exo* product.



### 4.3.1 Effect of the *N*-substituent upon cyclisation.

In the 5-*exo* atom transfer radical cyclisation of haloacetamides onto alkenes the *N*-substituent often affects the efficiency of the reaction.<sup>48</sup> Thus, we initially attempted the cyclisation of substrates (**119**, **126-129**) in order to ascertain if the *N*-alkyl substituent had any effect upon the cyclisation. Hence, reactions of substrates (**119**, **126-129**) were carried out using 30 mol% CuBr and 30 mol% (**132**) (TPA) in dichloromethane (0.12 M) at room temperature. After 1 hour, following work-up by passing through a silica plug, the corresponding *tert*-bromo 4-*exo* atom transfer products (**133-136**) were obtained in excellent yield (table 11).



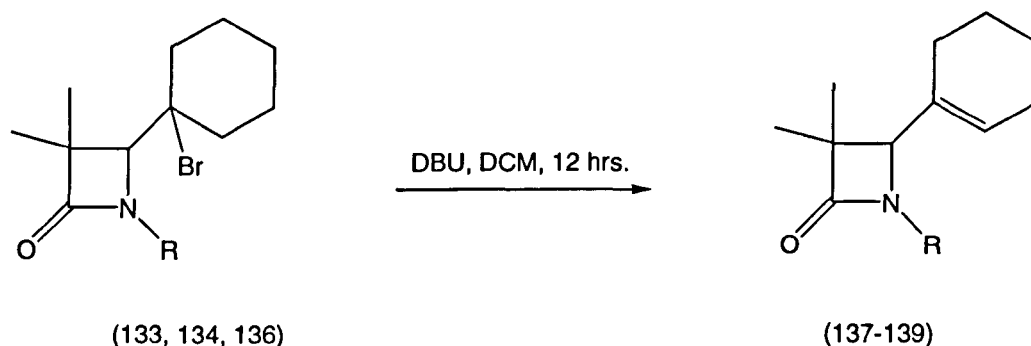
Substrate	R	Product	Yield
119	Bn	133	96%
126	PMB	134	98%
127	<i>t</i> -Bu	-	0
128	<i>i</i> -Bu	135	98%
129	<i>o</i> -Br-Bn	136	98%

Reaction of 128-129 required 2 hrs.

**Table 11.** Effect of enamide *N*-alkyl substituents upon cyclisation.

No products arising from 5-*endo* cyclisation or reduction of the initial radical were detected. However, the cyclisations of substrates (**128-129**) required 2 hours to go to completion indicating that the steric bulk of the *N*-alkyl group plays a role in determining the rate of cyclisation. In fact, the most hindered substrate (**127**) ( $R = t\text{-Bu}$ ) did not undergo cyclisation at all, even after extended reaction times (12 hours) under reflux in dichloroethane (80°C).

We found that the synthetic utility of the process can be expanded by manipulation of the tertiary bromide moiety. Thus, stirring bromides (**133**) ( $R = \text{Bn}$ ), (**134**) ( $R = \text{PMB}$ ) and (**136**) ( $R = o\text{-BrBn}$ ) with one equivalent of 1,8-diazabicyclo[5.4.0]-undecene (DBU) in dichloromethane at room temperature for 12 hours furnished the corresponding alkene products (**137-139**) in excellent yields (table 12).

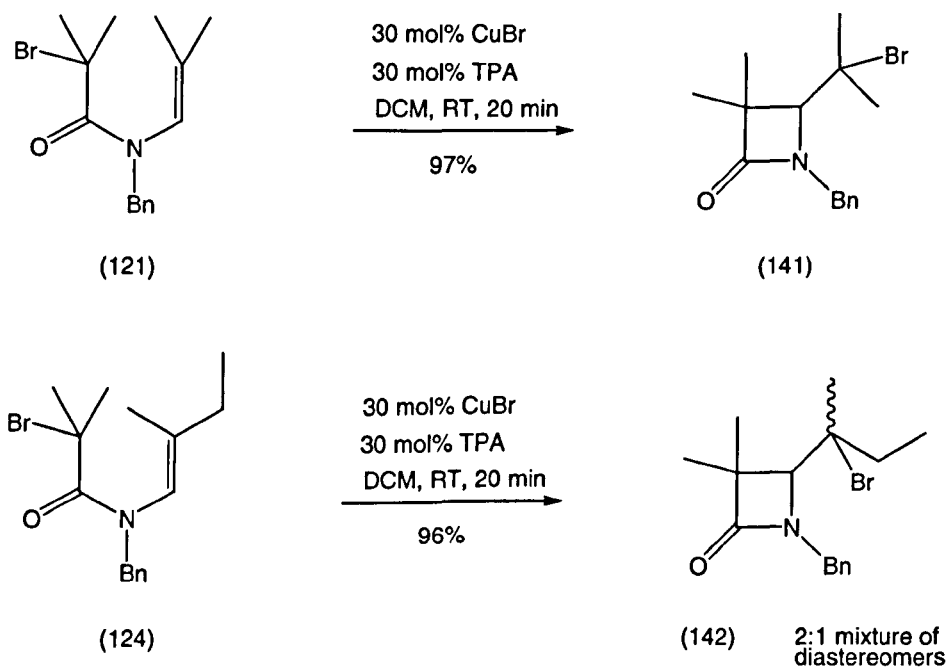


<i>tert</i> -Bromide	Elimination product (137-139)
133	94%
134	92%
136	98%

**Table 12.** Yields of  $\beta$ -lactam elimination products.

### 4.3.2 Effect of the enamide substituent.

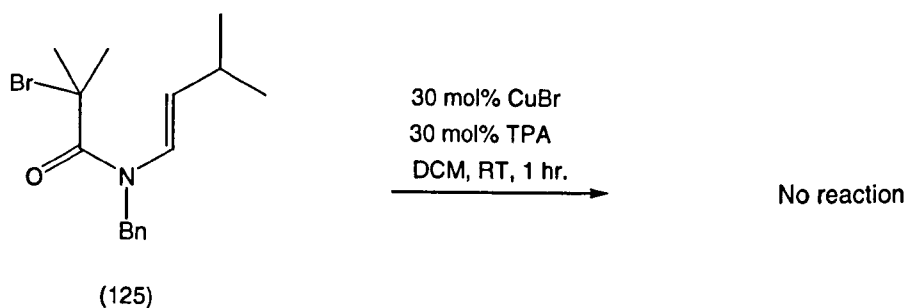
Having investigated the effect of the *N*-alkyl group we next turned our attention to the cyclisation of substrates in which we had varied the enamide substituents. We were pleased to discover that cyclisation of both **(121)** and **(124)** were extremely facile and gave rise to the corresponding bromo functionalised  $\beta$ -lactam products **(141-142)** within 20 minutes and again in excellent yield (scheme 71).



**Scheme 71.** CuBr(TPA) mediated cyclisation of enamides **(121)** and **(124)**.

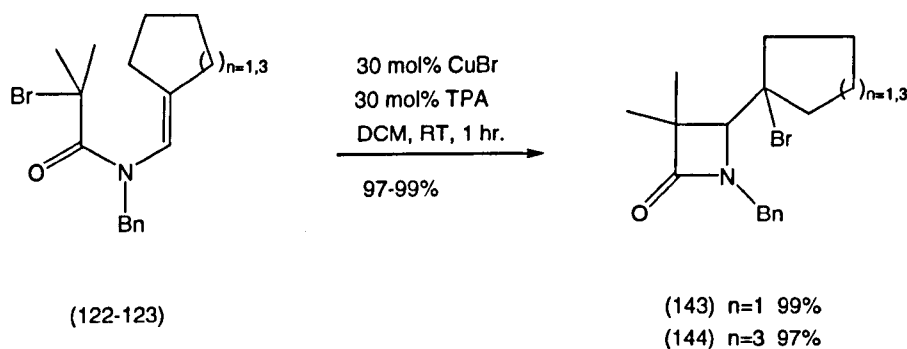
Note that the cyclisation of **(124)** furnished the tertiary bromide **(142)** as an inseparable 2:1 mixture of diastereomers. No attempt was made to determine which isomer was the major one.

Interestingly, cyclisation of the mono-substituted enamide (**125**) was not possible even after extended reactions times and at reflux (scheme 72). Only starting material was recovered from the reaction and no reduction of the substrate was detected.



**Scheme 72.** Attempted cyclisation of mono-substituted enamide (**125**).

The failure of this cyclisation demonstrates the importance of having two enamide substituents in stabilising the resulting 4-*exo* radical. Finally, we investigated the cyclisation of substrates (**122-123**) which contain a cyclopentyl and cycloheptyl ring appended to the alkene respectively (scheme 73).

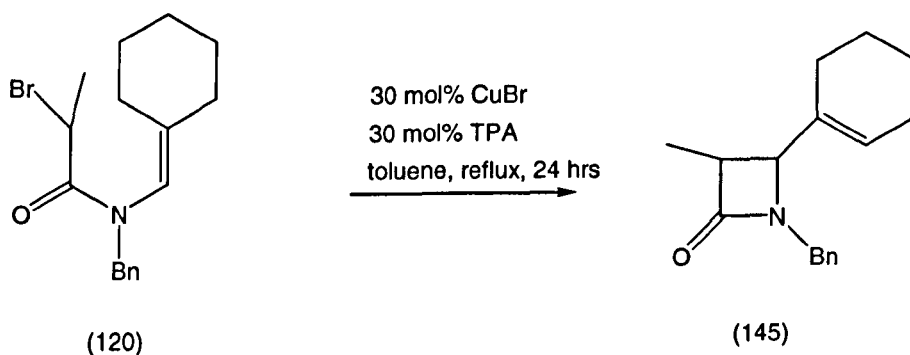


**Scheme 73.** Cyclisation of cyclopentyl and cycloheptyl enamide derivatives.

These too underwent cyclisation to give  $\beta$ -lactam products (**143-144**) exclusively.

#### 4.3.3 Further variation of substrate.

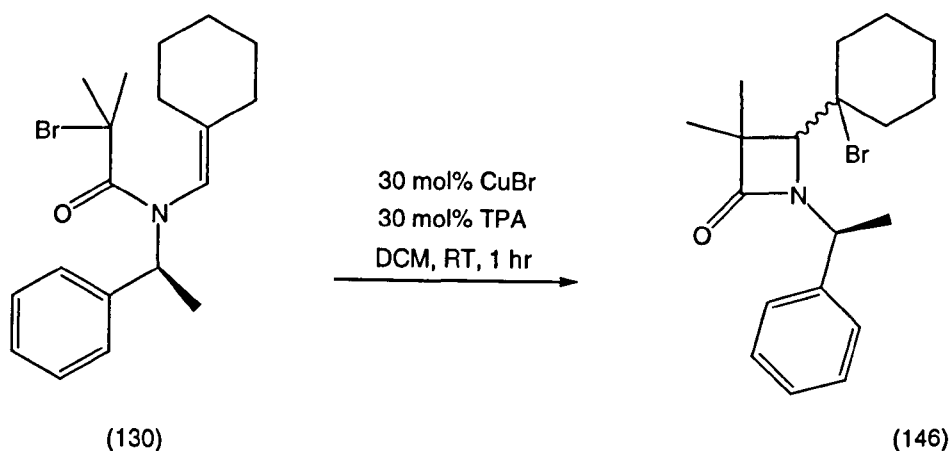
The cyclisation of secondary halides using atom transfer is often problematic and generally requires elevated temperatures, even with activated ligands (**131-132**). Thus, reaction of secondary bromide (**120**) with 30 mol% CuBr(TPA) in refluxing dichloromethane failed with only starting material being recovered. However, heating at a higher temperature in refluxing toluene (110°C) for 24 hours gave a 2.8:1 mixture of diastereomers (**145**) in 82% yield (scheme 74).



**Scheme 74.** Cyclisation of secondary bromide (**120**).

Elimination of the tertiary bromide occurred under these reaction conditions resulting in formation of the alkene (**145**) directly without the need for DBU mediated elimination (section 4.3.1). Again, no attempt was made to determine which isomer was the major product.

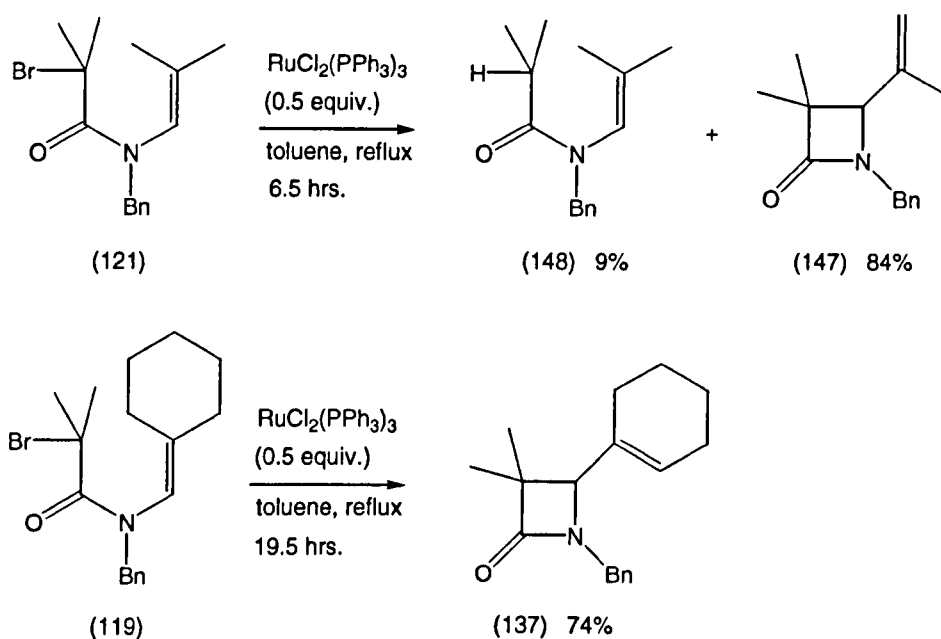
Finally, cyclisation of the chiral substrate (**130**) was examined. The reaction proceeded as expected to give a 0.8:1 ratio of diastereomers of the bromide (**146**) in 96% yield (scheme 75).



**Scheme 75. Reaction of chiral substrate (130).**

#### 4.4 Comparison of efficiency with reported ruthenium(II) atom transfer cyclisation catalyst.

The atom transfer cyclisation of bromo-enamides (**119**) and (**121**) with  $\text{RuCl}_2(\text{PPh}_3)_3$  has recently been reported.<sup>38</sup> Therefore, a comparison of the results obtained using our CuBr(TPA) system to those published by Ghelfi is given here. Ghelfi reported that reaction of bromide (**121**) with  $\text{RuCl}_2(\text{PPh}_3)_3$  (0.5 eq.) in refluxing toluene (110°C) for 6.5 hours resulted in a mixture of the unsaturated  $\beta$ -lactam (**147**) and reduction product (**148**). Cyclisation of the related precursor (**119**) gave the corresponding alkene (**137**) after 19.5 hours under the same conditions (scheme 76).



Scheme 76. Ruthenium(II) promoted cyclisation of bromo-enamides.

Substrate	AT Catalyst	Reaction Temp.	Reaction Time	Yield of $\beta$ -Lactam
119	$\text{CuBr}(\text{TPA})$ (0.3 eq.)	RT	1 hr.	(133) 96%
119	$\text{RuCl}_2(\text{PPh}_3)_3$ (0.5 eq.)	110°C	19.5 hrs.	(137) 74%
121	$\text{CuBr}(\text{TPA})$ (0.3 eq.)	RT	20 min.	(141) 97%
121	$\text{RuCl}_2(\text{PPh}_3)_3$ (0.5 eq.)	110°C	6.5 hrs.	(147) 84%

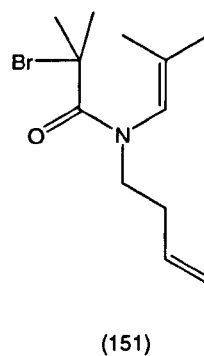
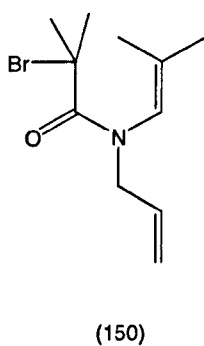
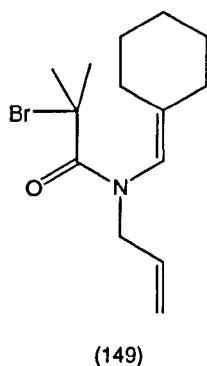
Table 13. Comparison between  $\text{CuBr}(\text{TPA})$  and  $\text{RuCl}_2(\text{PPh}_3)_3$  catalysts.

The results in table 13 clearly show that the  $\text{CuBr}(\text{TPA})$  system offers significant advantages over the use  $\text{RuCl}_2(\text{PPh}_3)_3$  enabling cyclisation under milder reaction conditions and in shorter times. In addition, elimination of hydrogen bromide results in

direct formation of the unsaturated  $\beta$ -lactams (**137**, **147**) further limiting the use of the ruthenium system.

#### 4.5 4-*Exo* versus 5-*exo* radical cyclisation.

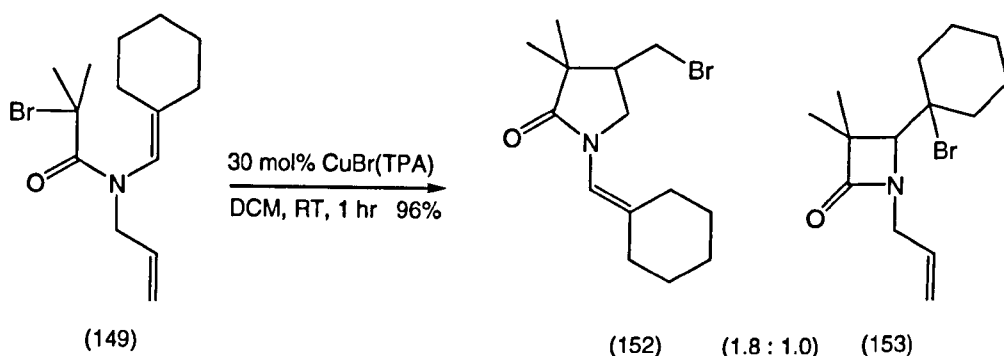
Finally, we were interested in investigating the reaction of substrates in which ring closure might occur in a 4-*exo* or 5-*exo* manner. Thus, the preparation of precursors (**149-151**) was conducted according to the procedures outlined in section 4.2.



For precursors (**149-150**) 4-*exo* cyclisation onto the enamide double bond might be expected to produce the kinetically favoured  $\beta$ -lactam, alternatively, 5-*exo* cyclisation onto the *N*-allyl group might give the thermodynamically more stable  $\gamma$ -lactam product. Therefore, by varying the reaction conditions we hoped to be able to control the regioselectivity of the cyclisation.

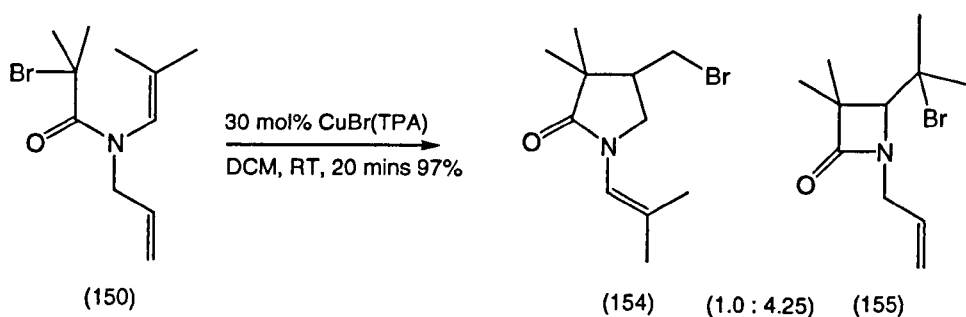


Reaction of **(149)** with 30 mol% CuBr(TPA) in dichloromethane at room temperature for 1 hour gave an inseparable mixture of  $\gamma$ -lactam **(152)** and  $\beta$ -lactam **(153)** in a ratio of 1.8:1 (scheme 77) (i.e. the  $\gamma$ -lactam was the major product).



**Scheme 77. CuBr(TPA) mediated cyclisation of (149).**

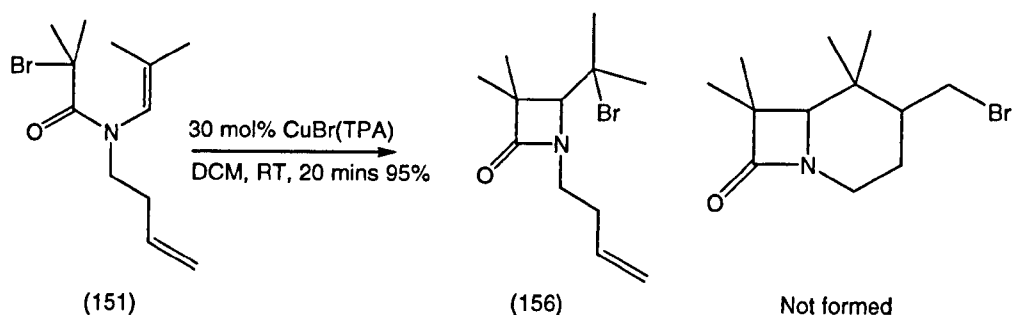
By repeating the reaction at a lower temperature and by using a higher catalyst concentration we hoped to increase formation of the kinetic 4-*exo* product **(153)**. However, reaction of **(149)** with 1 equivalent of CuBr(TPA) in dichloromethane at 0°C did not significantly alter the product distribution. Cyclisation of **(149)** with 3 mol% of CuBr(TPA) in toluene at 110°C was also attempted (in order to further promote formation of the thermodynamically more stable  $\gamma$ -lactam **(152)**) but failed due to solubility problems. We next turned our attention to the cyclisation of the related precursor **(150)**. Reaction with 30 mol% CuBr(TPA) in dichloromethane at room temperature for 20 minutes afforded a mixture of  $\gamma$ -lactam **(154)** and  $\beta$ -lactam **(155)** in a ratio of 1 : 4.25 (scheme 78).



**Scheme 78.** CuBr(TPA) mediated cyclisation of (150).

Interestingly, the regioselectivity of the reaction has now switched and the  $\beta$ -lactam (155) is now the major product. This is possibly due to the less hindered enamide (150) favouring formation of the 4-*exo* derived product. Repeating the reaction with 3 mol% CuBr(TPA) in dichloroethane at 80°C (in order to encourage formation of the thermodynamically stable  $\gamma$ -lactam) had little effect upon the product ratio. Overall, the inability to alter the product distributions suggests that interconversion between the two possible amide conformations is not rapid enough to allow control over regioselectivity.

Finally, reaction of (151) with 30 mol% CuBr(TPA) in dichloromethane at room temperature for 20 minutes furnished  $\beta$ -lactam (156) exclusively (scheme 79). In this case a much slower 6-*exo* cyclisation obviously can not compete with 4-*exo* ring closure. It was hoped that 6-*exo* cyclisation might then follow the initial 4-*exo* reaction to afford the corresponding bicyclic system. However, cyclisation of (151) with 1 equivalent of CuBr(TPA) in refluxing dichloroethane in a sealed tube for 48 hours resulted in formation of the monocyclised product (156) only.



**Scheme 79. CuBr(TPA) mediated cyclisation of (151).**

#### 4.6 Conclusions.

In conclusion, we have demonstrated that atom transfer cyclisation of terminally substituted enamides using a catalytic amount of CuBr(TPA) furnishes bromo-functionalised  $\beta$ -lactams in excellent yield (82-99%). Reactions proceeded via a 4-*exo* radical cyclisation and no products arising from 5-*endo* ring closure or reduction of the original radical precursors were detected. The efficient formation of the  $\beta$ -lactam products permits cyclisations to be conducted under extremely mild reaction conditions and offers distinct advantages over the use of RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>. It is generally accepted that the 4-*exo* cyclisation products are the kinetically derived products while those arising from 5-*endo* cyclisation are thermodynamically favoured. In this chapter we have shown that cyclising onto terminally substituted enamides (which will sterically impede 5-*endo* cyclisation), in conjunction with the use of a very active atom transfer catalyst (that allows rapid trapping of the intermediate radicals at ambient temperature) favours the

formation of the kinetic  $\beta$ -lactam products. Interestingly, even at 110°C in toluene, cyclisation of secondary bromide (**120**) furnished the 4-*exo* product exclusively thus highlighting the efficient nature of the atom transfer catalyst used in trapping out the intermediate cyclised radical.

#### 4.7 Future work.

Work is currently underway within the group to apply this methodology towards the synthesis of  $\beta$ -lactam derived natural products that are of biological interest. In order for this work to be successful investigation into a reliable method for the deprotection of *N*-benzylamide type cyclisation products is a priority.

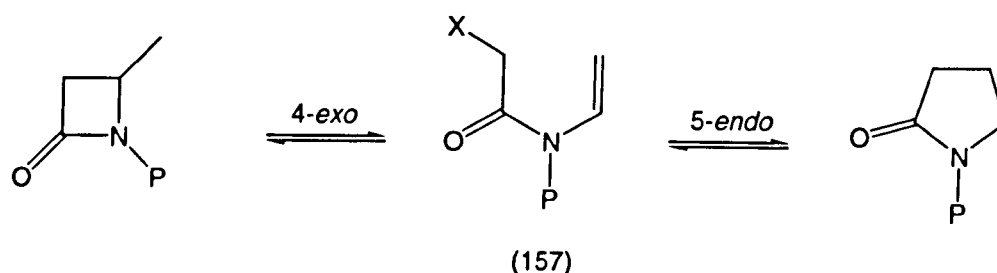
## Chapter 5

### Lycorane and Erythrinane Skeleton Synthesis Via 5-Endo

#### Radical Cyclisation

##### 5.1 Introduction.

In recent years considerable attention has been directed towards the use of free-radical cyclisation reactions for the synthesis of nitrogen-containing heterocycles.<sup>26b</sup> Thus, a wide range of *N*-allyl-haloacetamides are known to undergo 5-*exo* radical cyclisation via a carbamoyl radical to give five-membered lactam products.<sup>2-5</sup> The potential utility of this methodology in the field of natural product synthesis was initially illustrated by application to the synthesis of pyrrolizidine and *Sceletium* alkaloids.<sup>51</sup> Radical cyclisation protocols have subsequently been applied to a much wider range of bi- and poly-cyclic nitrogen heterocycles<sup>25</sup> and can now be envisaged for synthetic use in most ring systems. In the previous chapter we examined the mode of cyclisation of halo-enamide substrates. In principle, the ring closure of substrate (157) may either occur in a 4-*exo* or 5-*endo* manner (scheme 80). However, halo-enamides (157) preferentially undergo the disfavoured 5-*endo* mode of ring closure, although, we have demonstrated that suitably designed precursors can be used to encourage 4-*exo* cyclisation.

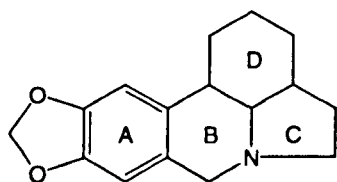


**Scheme 80. 4-Exo versus 5-endo cyclisation of halo-enamides.**

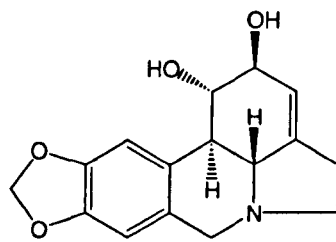
Consequently, we propose to prepare a range of fused five-membered lactams *via* copper(I) mediated *5-endo* atom transfer radical cyclisation of halo-*N*-(cycloalk-1-enyl)acetamides, and investigate the feasibility of this method for the synthesis of the lycorane and erythrinane skeletons.

### 5.1.1 The lycorine family.

The lycorine-type *Amaryllidaceae* alkaloids (e.g. (159)) are characterised by the presence of the galanthane ring system (158). Many of these alkaloids display potentially useful biological properties including antiviral, antineoplastic and antimitotic activity.<sup>52</sup> Others are known to inhibit plant growth and disrupt peptide bond formation in protein synthesis.  $\gamma$ -Lycorane (159) itself does not appear to possess any useful pharmacological properties. However, it has become a popular synthetic target as its pentacyclic structure provides a means of demonstrating the utility of new synthetic strategies.



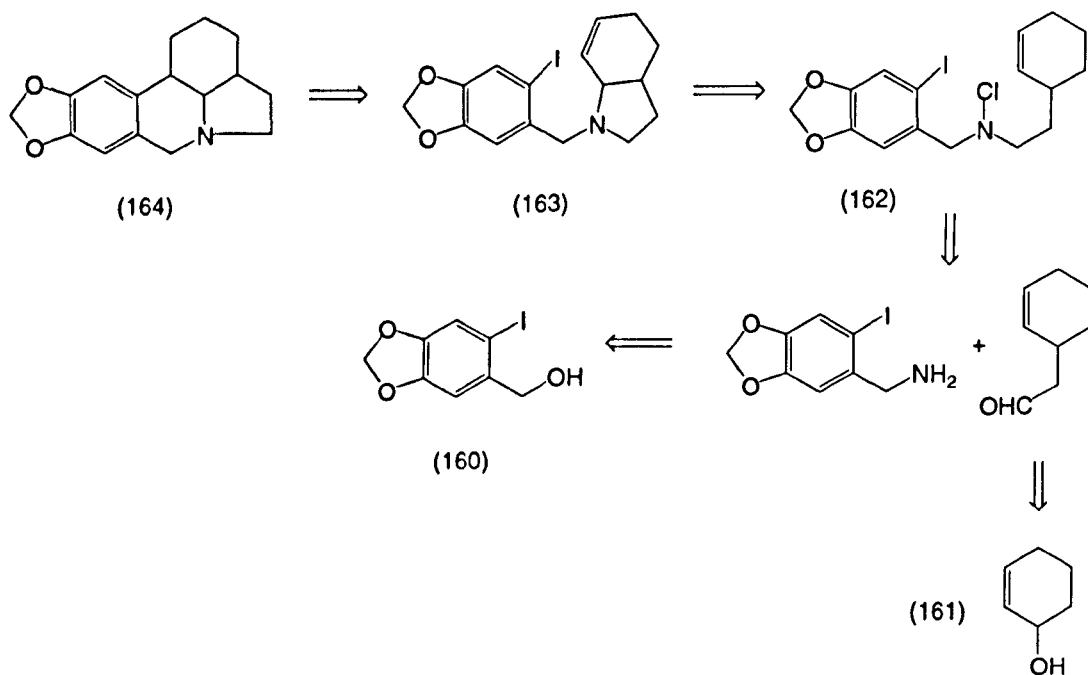
(158)



(159)

### 5.1.2 Radical approaches towards the Lycorane ring system.

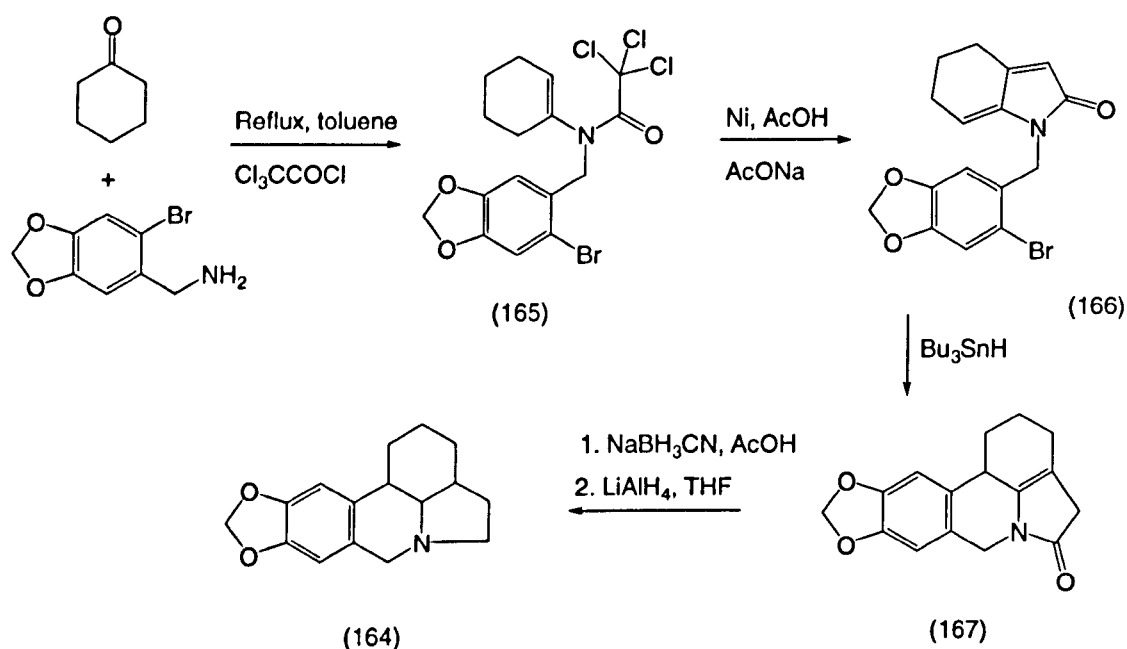
Cossy *et al*<sup>53</sup> have reported a ten step procedure for the synthesis of  $\gamma$ -lycorane from the piperonylic alcohol (160) and cyclohex-2-enol (161) involving radical cyclisations for the formation of the B and C rings (158) (scheme 81).



Scheme 81. Synthesis of lycorane skeleton (164) as reported by Cossy *et al*.

Thus, precursor (**162**) (prepared *via* a seven step synthesis) underwent cyclisation with  $\text{CuCl/CuCl}_2$  in  $\text{THF/H}_2\text{O/AcOH}$  to afford the C ring (**163**). Following elimination with DBU, intermediate (**163**) then underwent a tributyl tin mediated radical cyclisation to give the B ring and hence the desired product (**164**).

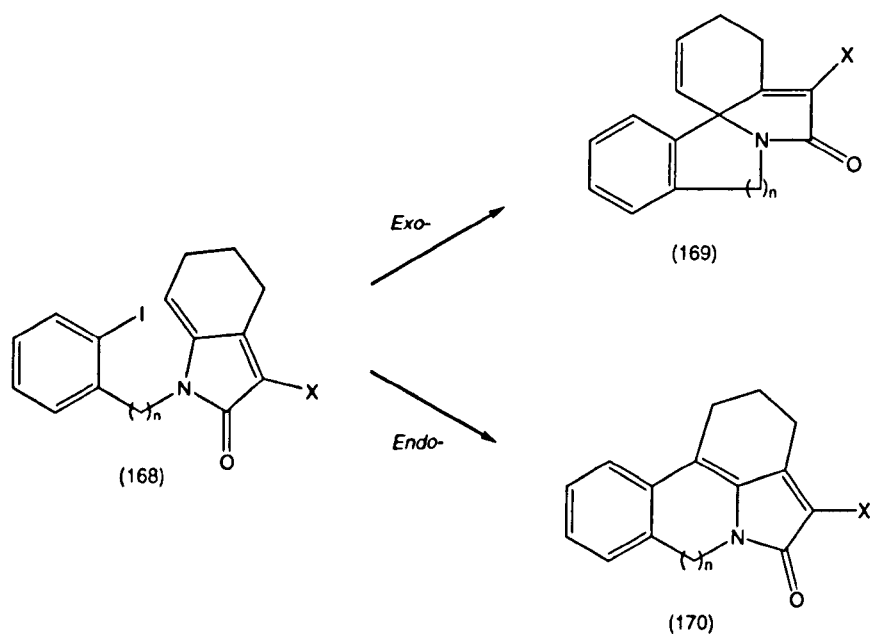
A four step synthesis of racemic  $\gamma$ -lycorane has also been reported by Zard.<sup>54</sup> Formation of the key C ring was accomplished using a nickel/acetic acid promoted *5-endo* radical cyclisation to give (**166**). Again, a tin mediated *6-endo* radical cyclisation was then used to furnish the B ring (**167**). Reduction of (**167**) using sodium cyanoborohydride then  $\text{LiAlH}_4$ , to remove the carbonyl, gave  $\gamma$ -lycorane (**164**) (scheme 82).



**Scheme 82.** Synthesis of lycorane skeleton (**164**) reported by Zard.



The syntheses of  $\gamma$ -lycorane (**164**) described above both utilise an organotin mediated cyclisation for the formation of the B ring. However, Rigby *et al*<sup>55</sup> have reported use of a selective intramolecular Heck process for the formation of both the lycorane and erythrinane skeletons. Thus, *endo*-cyclisation of (**168**) ( $n=1$ ) forms the lycorane system (**170**), while the *exo* pathway (with  $n=2$ ) afforded the erythrinane skeleton (**169**) (scheme 83).

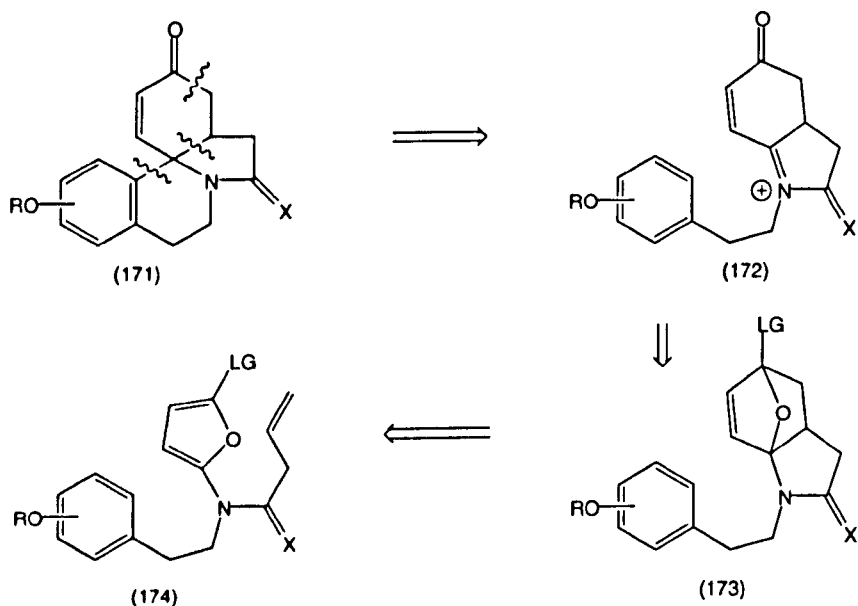


**Scheme 83. Cyclisation pathways in the intramolecular Heck reaction of (**168**)**

It was reported that the use of standard Heck conditions ( $\text{Pd}(\text{OAc})_2$  (10 mol%), (*o*-tol) $_3\text{P}$  (20 mol%),  $\text{Et}_3\text{N}$  (2 eq.),  $\text{MeCN}/\text{H}_2\text{O}$ ,  $80^\circ\text{C}$ ) afforded mainly the *exo* derived product (**169**), while use of the Jeffery palladium catalyst system ( $\text{Pd}(\text{OAc})_2$  (10 mol%), *n*- $\text{Bu}_4\text{NCl}$  (2 eq.),  $\text{KOAc}$  (5.5 eq.),  $\text{DMF}$   $100^\circ\text{C}$ ) provided the product of the *endo* pathway (**170**) exclusively.

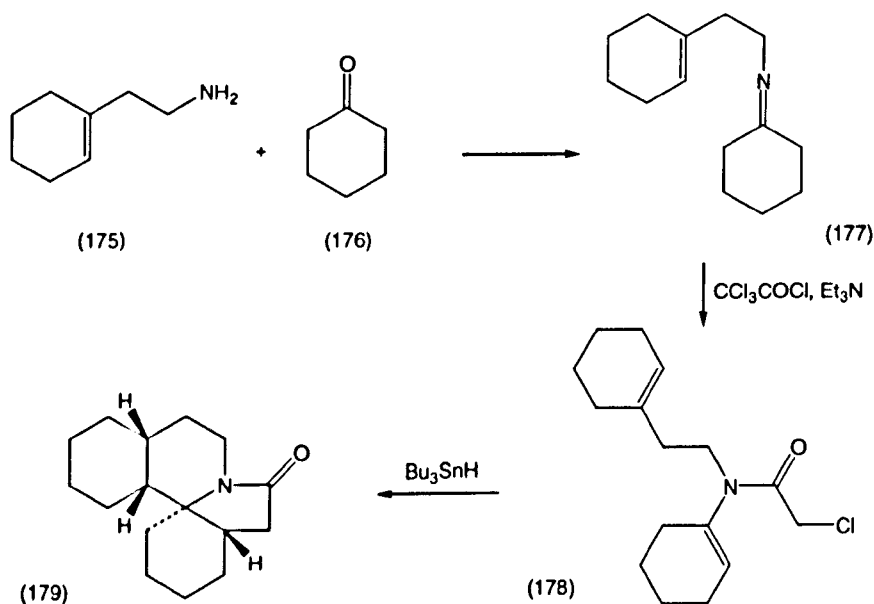
### 5.1.3 The Erythrinane Family

The *Erythrina* alkaloids are a large family of biologically active natural products.<sup>56</sup> Many erythrinane compounds possess curare-like activity and their extracts have been used in indigenous medicine.<sup>57</sup> A variety of pharmacological effects including sedative, hypotensive, neuro-muscular blocking and CNS depressant properties are also associated with the erythrinane skeleton.<sup>58</sup> The vast majority of naturally occurring erythrina alkaloids possess a tetracyclic framework and, like the lycorane family, numerous synthetic approaches into the erythrina ring system have been developed. Padwa has reported a triple cascade reaction sequence<sup>59</sup> involving an intramolecular Diels-Alder reaction to form cycloadduct (**173**). This then undergoes ring-opening to generate the acyliminium ion (**172**) followed by cyclisation to give (**171**). Thus, using this approach the ring system (**171**) is assembled in a single operation (**174**→**171**) (scheme 84).



**Scheme 84.** Cascade sequence for construction of the erythrinane skeleton.

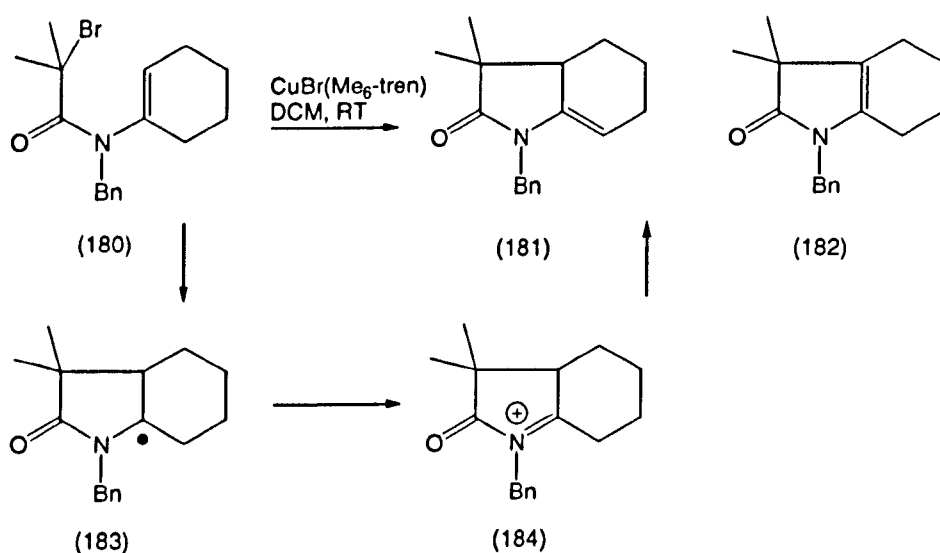
Ikeda has reported a  $\text{Bu}_3\text{SnH}$ -mediated radical cyclisation approach into the erythrinane skeleton.<sup>60</sup> Thus, condensation of 2-(cyclohex-1-enyl)ethylamine (**175**) and cyclohexanone (**176**) formed the imine (**177**), which was subsequently treated with chloroacetyl chloride and triethylamine to afford the cyclisation precursor (**178**). Enamide (**178**) then underwent cyclisation in the presence of  $\text{Bu}_3\text{SnH}$  and AIBN to furnish the erythrinane skeleton (**179**) (scheme 85).



**Scheme 85.**  $\text{Bu}_3\text{SnH}$ -mediated radical cyclisation leading to erythrinane (**179**)

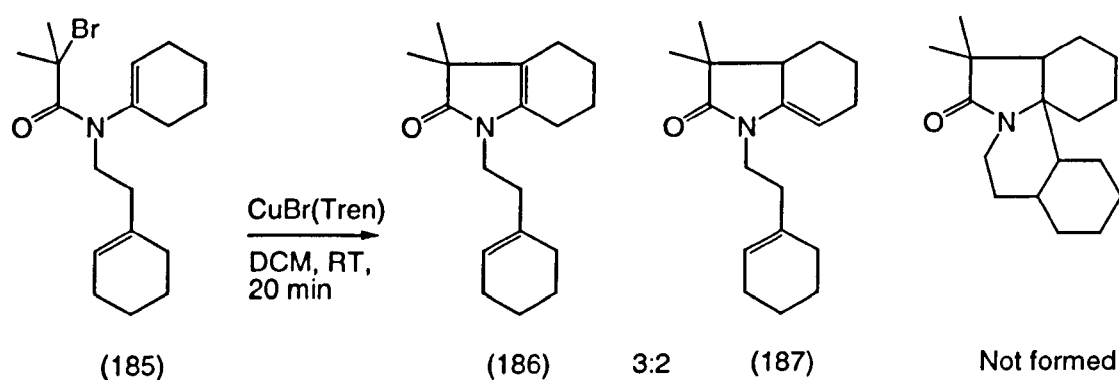
## 5.2 Work previously conducted within the Clark group.

A range of bicyclic lactam compounds have been synthesised within the group *via* the less common *5-endo* mode of radical cyclisation.<sup>42</sup> Thus, monobromo-enamide (**180**) underwent cyclisation with 30 mol% CuBr(Me<sub>6</sub>-tren) in dichloromethane at room temperature to furnish two alkene products (**181-182**) in 82% yield (1:1 ratio) (scheme 86). Mechanistically, the reaction has been proposed to occur *via* an initial *5-endo* radical cyclisation to give (**183**) followed by Cu(II) mediated oxidation of the tertiary radical to the corresponding *N*-acyl iminium ion (**184**). Elimination of a proton then affords the two regioisomers (**181-182**).



Scheme 86 Copper mediated *5-endo* cyclisation: radical/polar crossover mechanism.

We were interested to see if intramolecular capture of radical **(183)** (such as in a tandem cyclisation process) could compete with the oxidation step. Therefore, by introducing a cyclohexenyl-based *N*-protecting group, it was hoped that an electrophilically triggered 6-*endo* cyclisation might follow the initial 5-*endo* reaction to afford the B and C rings of the lycorane or erythrinane skeleton. However, cyclisation of **(185)** resulted in a mixture of regioisomers of the monocyclised product **(186)** and **(187)** only<sup>42</sup> (scheme 87).

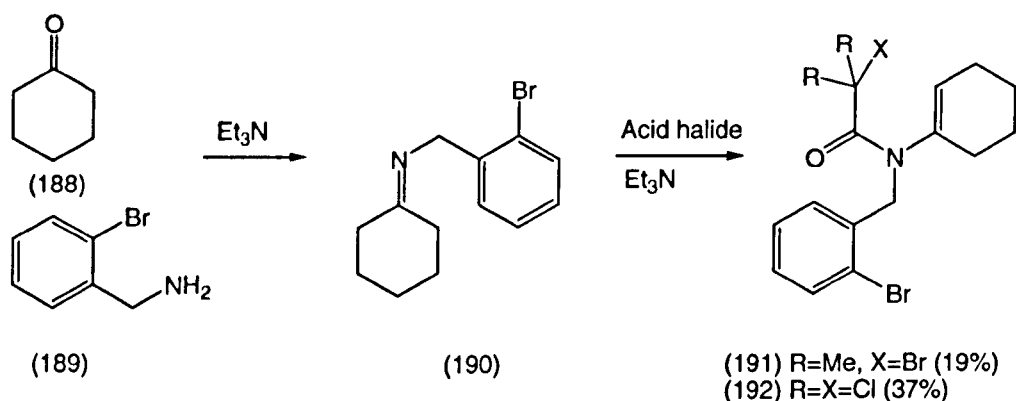


**Scheme 87. Attempted CuBr(Me<sub>6</sub>-tren) mediated tandem cyclisation reaction.**

Clearly, oxidation of the initial radical is faster than capture *via* 6-*endo* cyclisation. Therefore, we decided to adapt the *N*-group of the cyclisation precursor to include a phenyl ring with a halogen atom in the 2-position. This might then be expected to undergo a Heck type palladium coupling as reported by Rigby<sup>55</sup> to form the B ring of the lycorane or erythrinane system. If successful, the aromatic protecting group could then be replaced by a piperonylic alcohol **(160)** derived amine to form the  $\gamma$ -lycorane skeleton.

### 5.3 Lycorane precursor synthesis.

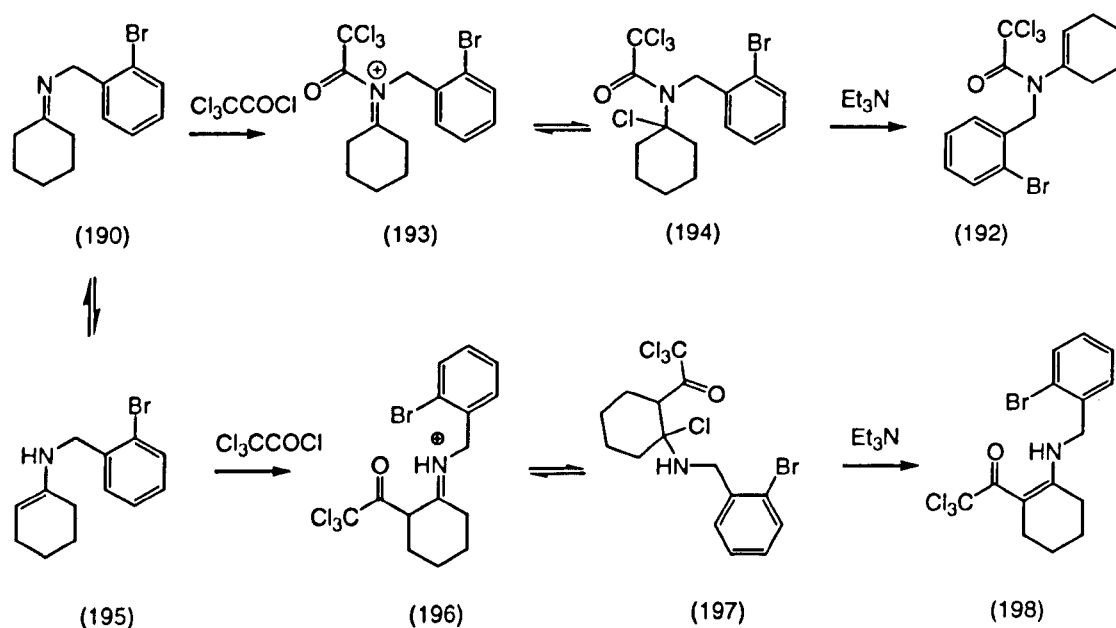
The preparation of cyclisation precursors (**191-192**) was carried out according to standard literature procedures. Thus, a solution of 2-bromobenzylamine (**189**) and cyclohexanone (**188**) in toluene were heated at reflux in a Dean-Stark apparatus with azeotropic removal of water for 4 hours. The solvent was then removed under reduced pressure to yield the imine (**190**) (scheme 88).



**Scheme 88. Synthesis of lycorane skeleton cyclisation precursors.**

The appropriate acid chloride/bromide was then added dropwise and the mixture was stirred for 1 hour at room temperature. After cooling to  $0^\circ\text{C}$ , triethylamine (3.0 eq.) was added and the mixture was stirred for a further 2 hours at room temperature. Following work-up, purification by column chromatography afforded halo-enamides (**191**) and (**192**). The relatively poor yields obtained for precursor (**191-192**) may be attributed to competition between *N*-acylation and *C*-acylation of the imine (**190**).

Hence, imine (190) may undergo *N*-acylation via the *N*-acyliminium ion (193) to afford the desired trichloroacetamide (192). Alternatively, the corresponding enamine (195) can undergo *C*-acylation to give the iminium ion (196). This exists in equilibrium with adduct (197) which upon treatment with triethylamine affords the *C*-acylated by-product (198) (scheme 89).

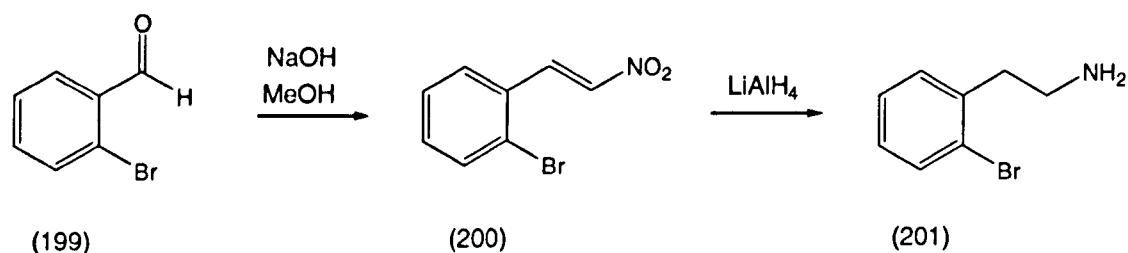


**Scheme 89. Competing *N*-acylation and *C*-acylation pathways.**

Significant amounts of the *C*-acylated by-products were isolated during the preparation of both (191) and (192), interestingly this problem was not encountered during the preparation of enamides described in section 4.2.

## 5.4 Erythrinitol precursor synthesis.

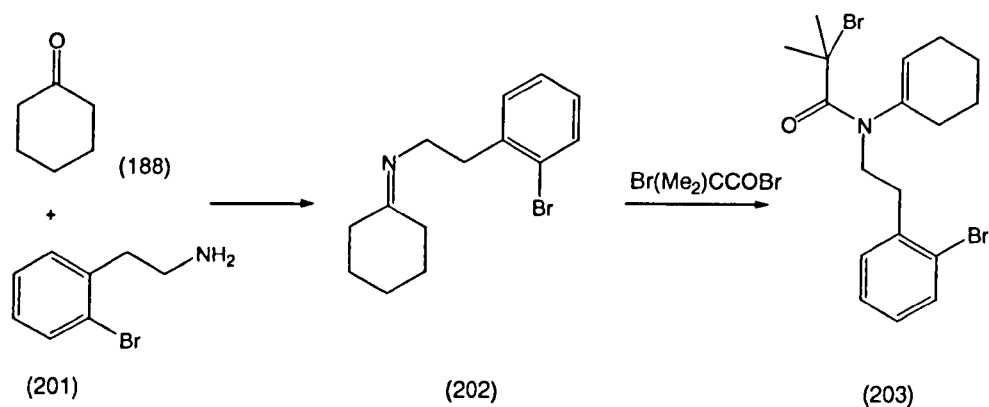
In order to form the erythrinane alkaloid skeleton the *N*-group of the cyclisation precursor must contain an additional CH<sub>2</sub> group. The corresponding amine (**201**) was not available commercially and was therefore synthesised in a two-step procedure<sup>61</sup> from 2-bromobenzaldehyde (**199**). Thus, an aqueous solution of sodium hydroxide was added to a solution of bromobenzaldehyde (**199**) and nitromethane in methanol. The mixture was stirred at room temperature for 1 hour and then added to an excess of hydrochloric acid to deposit the crude product (**200**). Subsequent recrystallisation from ethanol afforded 2-bromonitrostyrene (**200**) as pale yellow pillars in 73% yield. Reduction of the double bond and nitro group with lithium aluminium hydride then gave 2-(2-bromo-phenyl)-ethylamine (**201**) in 96% yield (scheme 90).



**Scheme 90. Preparation of 2-(2-bromo-phenyl)-ethylamine.**

2-(2-Bromo-phenyl)-ethylamine (**201**) and cyclohexanone (**188**) were then converted to the imine (**202**) by refluxing in toluene with azeotropic removal of water. Acylation with 2-bromo-2-methyl-propionyl bromide was then conducted as previously described (section 5.3) to afford the monobromo-acetamide (**203**) in 22% yield (scheme 91).

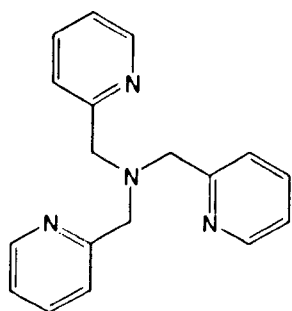




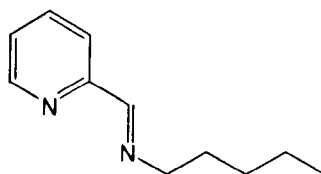
Scheme 91. Preparation of erythrinane precursor (203).

## 5.5 Cyclisation reactions.

We initially investigated the cyclisation of the monobromoacetamide lycorane skeleton precursor (191). Thus, cyclisation of (191) was attempted with 30 mol%  $\text{CuBr}(\text{NPMI})$  in dichloromethane at room temperature. However, after 48 hours only starting material was recovered. We therefore repeated the reaction using the more active tripyridyl amine (TPA) ligand.

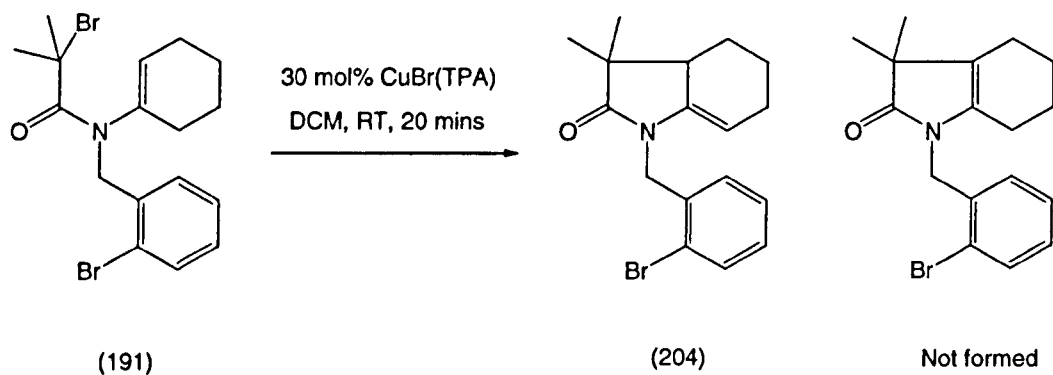


Tripyridyl amine (TPA)



N-pentyl-2-pyridylmethanimine (NPMI)

We were encouraged to find that reaction of **(191)** with 30 mol% CuBr(TPA) in dichloromethane (0.12M) at room temperature afforded the bicyclic lactam **(204)** in 90% yield after just 20 minutes (scheme 92).

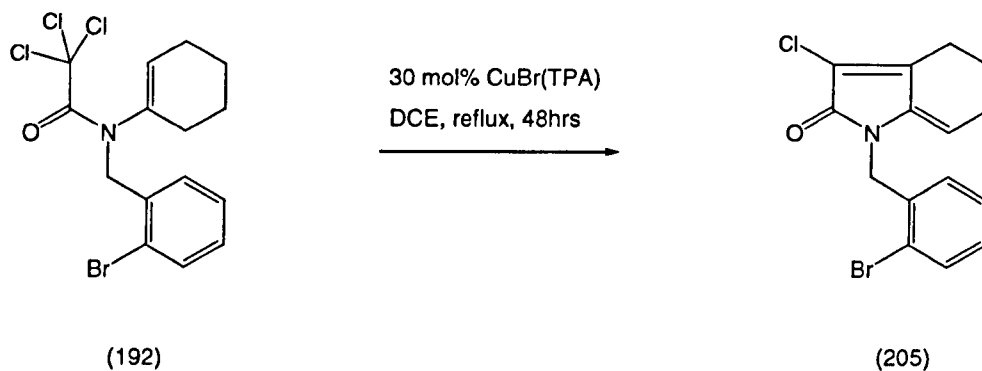


**Scheme 92. Cyclisation of monobromoacetamide (191).**

Interestingly, the expected mixture of regioisomers was not observed (*cf.* scheme 86) and cyclisation resulted in exclusive formation of the alkene product **(204)**. This is advantageous since the double bond in the six-membered ring of **(204)** is in an ideal position for palladium coupling to occur and therefore the difficult separation of regioisomers is not required.

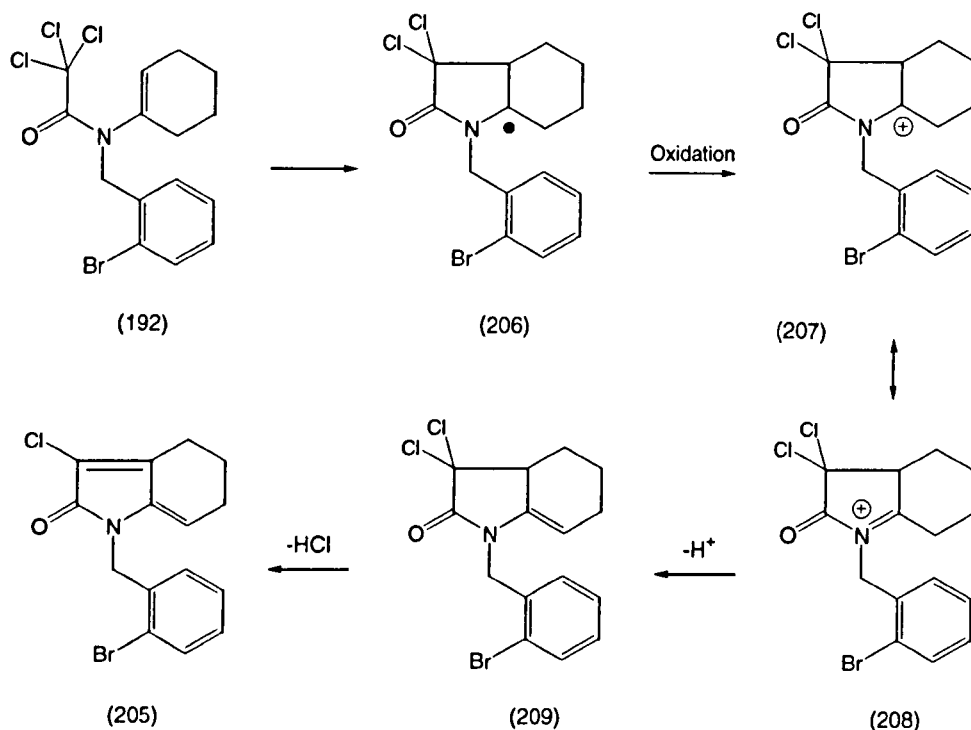
Next we turned our attention to the cyclisation of the trichloroacetamide precursor **(192)**. Reaction of **(192)** with 30 mol% CuCl(TPA) in dichloromethane (0.12M) at room temperature failed with only starting material being recovered after 24 hours.

More forcing conditions were required thus, precursor (**192**) and CuCl(TPA) were heated under reflux in 1,2-dichloroethane at 80°C for 48 hours. Following purification by column chromatography, the diene (**205**) was isolated in 62% yield (scheme 93).



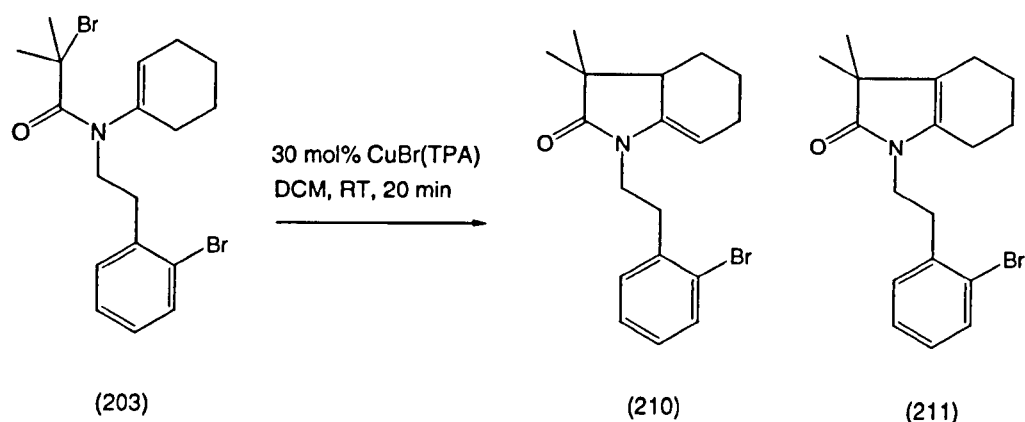
**Scheme 93. Cyclisation of trichloroacetamide (192).**

Formation of diene (**205**) is thought to result from Cu(II) mediated oxidation of cyclised radical (**206**) to give the corresponding *N*-acyl iminium ion (**208**) via cation (**207**). Subsequent elimination of a proton followed by elimination of HCl then affords the observed product (**205**) (scheme 94). The double bond in the six membered ring of (**205**) is again ideally positioned for palladium coupling to give the B ring of the lycorane skeleton.



Scheme 94. Formation of diene (205).

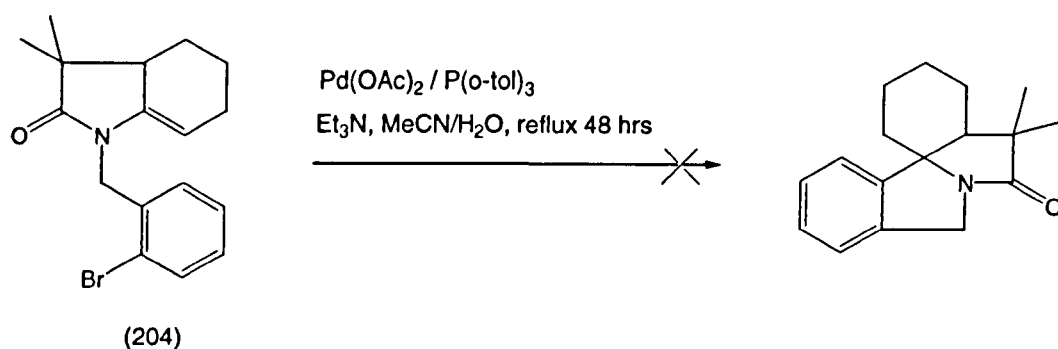
Finally, cyclisation of the monobromoacetamide erythrinane skeleton precursor (203) was carried out with 30 mol% CuBr(TPA) in dichloromethane (0.12M) at room temperature. After 20 minutes the reaction had gone to completion to give a 1:1 mixture of regioisomers (210) and (211) (scheme 95). The separation of regioisomers was problematic and only a very small amount of cyclic product (211) was isolated pure (8%). Therefore further investigation of palladium coupling methods to give the erythrinane skeleton was not undertaken.



**Scheme 95. Cyclisation of monobromoacetamide (203).**

## 5.6 Palladium coupling reactions.

Following atom transfer cyclisation, the standard Heck palladium coupling method utilised by Rigby<sup>55</sup> was applied to (204) in an attempt to form the lycorane skeleton. Thus, (204) was heated under reflux with 10 mol% Pd(OAc)<sub>2</sub> and 20 mol% tri-*o*-tolylphosphine with triethylamine in acetonitrile and water (10:1) for 48 hours at 85 °C. However, the reaction failed with only starting material recovered (scheme 96). The reaction was repeated using the Jeffery palladium catalyst system (Pd(OAc)<sub>2</sub> (10 mol%), *n*-Bu<sub>4</sub>NCl (2 eq.), KOAc (5.5 eq.), DMF (0.2M), 100 °C, 48 hours) and was also unsuccessful. Reaction of the related precursor (205) to give the lycorane skeleton also failed using both palladium coupling methods with only starting material being recovered.



**Scheme 96. Attempted formation of lycorane skeleton.**

Rigby *et al* used iodine rather than bromine at the 2-position of the phenyl ring in their synthesis of lycorane. It is known<sup>55</sup> that palladium acetate facilitates coupling with iodine more readily than bromine and this may account for the failure of these reactions. Other reported syntheses of the lycorane and erythrinane skeletons utilise tin-mediated radical cyclisations for formation of the B ring. However, the use of this reagent would negate many of the advantages associated with the copper(I) methodology and was therefore not used to complete the synthesis. For this reason further work to adapt the palladium coupling method in order to find more successful conditions would be required to complete this work.

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## **Chapter 6**

### **Experimental**

#### **6.1 General Experimental.**

Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 1720X fourier transform spectrometer either in a solution cell, as Nujol mulls or neat as stated in the text, with only selected absorbances ( $\nu_{\max}$ ) being reported.  $^1\text{H}$  NMR spectra were obtained using either a Bruker ACF 250, Bruker DPX 300 or Bruker DPX 400 at 250MHz, 300MHz or 400MHz respectively as stated in the text.  $^{13}\text{C}$  NMR were recorded at either 62.9MHz, 75.5MHz or 100.6MHz on a Bruker ACF 250, Bruker DPX 300 or Bruker DPX 400 respectively as stated in the text. Chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) and referenced to the appropriate solvent peak. Coupling constants ( $J$ ) are quoted in Hertz (Hz). Mass spectra were recorded on either a Kratos MS80 spectrometer or a Micromass Autospec spectrometer at the University of Warwick. Chemicals were purchased from Sigma-Aldrich, Lancaster or Fluka. Solvents were purchased from Fisons Scientific Equipment at SLR grade. Anhydrous solvents were obtained as follows: dry toluene, dichloromethane, diethyl ether and methanol were purchased from Romil. Tetrahydrofuran was distilled from sodium-benzophenone under

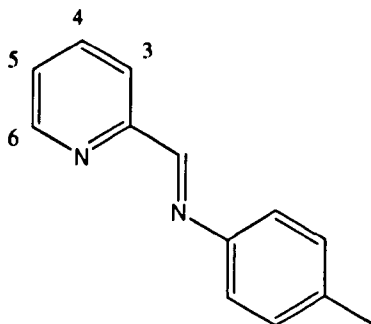
nitrogen. Thin layer chromatography (TLC) was conducted using Kieselgel 60F<sub>254</sub>, 0.2mm silica aluminium backed plates and developed using UV fluorescence (254nm), potassium permanganate solution or phosphomolybdic acid. Flash column chromatography was carried out on Merck Kieselgel 60F<sub>254</sub>, 230-400 mesh silica gel.

## 6.2 Experimental for chapter 2.

### 6.2.1 General procedure for the preparation of 2-pyridylmethanimine based ligands.

To a stirred solution of pyridinecarboxaldehyde in diethyl ether containing copious anhydrous magnesium sulfate was added amine (1 eq.). The resulting mixture was stirred overnight at room temperature. The magnesium sulfate was removed by filtration and the solvent removed under reduced pressure.

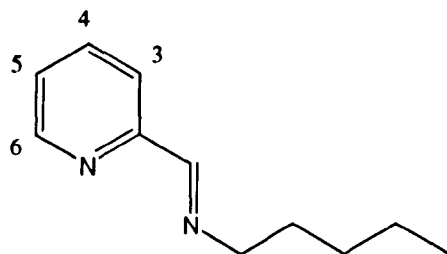
#### 6.2.1.1 Pyridin-2-ylmethylene-*p*-tolyl-amine (64b)<sup>1</sup>



2-pyridinecarboxaldehyde (0.88 ml, 9.33 mmol) and *p*-toluidine (1.03 ml, 9.33 mmol) were reacted as described above (6.2.1) to yield pyridin-2-ylmethylene-*p*-tolyl-amine (**64b**) (1.60 g, 88%) as yellow crystals. Spectral details match those previously reported.<sup>1</sup>

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 2922, 1626, 1581, 1565, 1504, 1462, 1433, 1376, 821, 737;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.76 (3H, s, **CH**<sub>3</sub>), 6.66 (4H, br s, aromatic H), 6.72 (1H, ddd, *J* 7.5, *J* 5.0, *J* 1.0, H-4), 7.14-7.20 (1H, app dt, *J* 7.5, *J* 1.5, H-5), 7.58 (1H, d, *J* 7.5, H-6), 8.01 (1H, s, **CH=N**), 8.07-8.09 (1H, m, H-3);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 20.86 (q), 120.90 (2 x d), 121.57 (d), 125.11 (d), 129.64 (2 x d), 136.03 (d), 136.41 (s), 148.09 (s), 149.44 (d), 154.47 (s), 159.45 (d).

#### 6.2.1.2 Pentylpyridin-2-ylmethyleneamine (**54a**)<sup>2</sup>

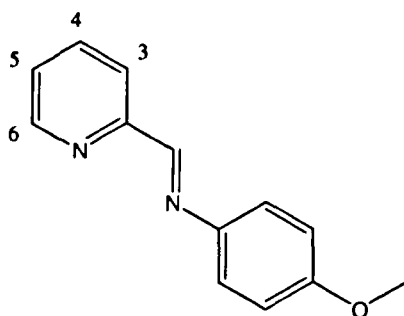


2-pyridinecarboxaldehyde (1.77 ml, 18.0 mmol) and *n*-pentylamine (2.16 ml, 18.0 mmol) were reacted as described above (6.2.1) to yield pentylpyridin-2-ylmethyleneamine (**54a**) (2.94g, 94%) as a pale yellow oil which was used without further purification. Spectral details match those previously reported.<sup>2</sup>

$\nu_{\max}$  (film) /cm<sup>-1</sup>; 3056, 2959, 2932, 2873, 1717, 1650, 1588, 1468, 1436, 1333, 1045, 992;  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>) 0.83 (3H, t, *J* 7.0, **CH**<sub>3</sub>), 1.25-1.30 (4H, m, **CH**<sub>2</sub>**CH**<sub>2</sub>**CH**<sub>2</sub>**CH**<sub>3</sub>),

1.63-1.68 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.59 (2H, t,  $J$  7.0,  $\text{NCH}_2\text{CH}_2$ ), 7.21 (1H, t,  $J$  5.5, H-4), 7.64 (1H, t,  $J$  7.5, H-5), 7.92 (1H, d,  $J$  7.5, H-6), 8.30 (1H, s,  $\text{CH}=\text{N}$ ), 8.57 (1H, d,  $J$  4.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 12.32 (q), 22.63 (t), 29.92 (t), 30.67 (t), 62.43 (t), 121.57 (d), 124.98 (d), 136.91 (d), 149.78 (d), 155.00 (s), 162.14 (d);  $m/z$  (EI) 177 ( $\text{MH}^+$ , 37%), 146 (13), 119 (100); (Found:  $\text{MH}^+$ , 177.1397.  $\text{C}_{11}\text{H}_{16}\text{N}_2$  requires  $\text{MH}^+$ , 177.1392).

### 6.2.1.3 (4-Methoxy-phenyl)-pyridin-2-ylmethylene-amine (64c)<sup>3</sup>



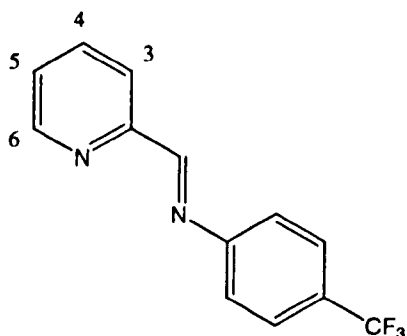
2-pyridinecarboxaldehyde (0.88 ml, 9.33 mmol) and *p*-anisidine (1.14g, 9.33 mmol) were reacted as described above (6.2.1) to yield (4-methoxy-phenyl)-pyridin-2-ylmethylene-amine (**64c**) (1.8 g, 93%) as a colourless oil. Spectral details match those previously reported.<sup>3</sup>

$\nu_{\text{max}}$  (neat)  $/\text{cm}^{-1}$  3003, 2932, 2834, 1712, 1624, 1580, 1504, 1466, 1298, 1245, 1033, 830, 762;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 3.84 (3H, s,  $\text{OCH}_3$ ), 6.95 (2H, d,  $J$  9.0, aromatic H), 7.27-7.36 (1H, m, H-4), 7.34 (2H, d,  $J$  9.0, aromatic H), 7.77-7.82 (1H, app dt,  $J$  8.0,  $J$  1.5, H-5), 8.19 (1H, d,  $J$  8.0, H-6), 8.64 (1H, s,  $\text{CH}=\text{N}$ ), 8.69-8.71 (1H, m, H-3);  $\delta_{\text{C}}$ (75.5



MHz, CDCl<sub>3</sub>) 55.89 (q), 114.84 (2 x d), 122.06 (d), 123.07 (2 x d), 125.23 (d), 137.03 (d), 144.06 (s), 150.04 (d), 155.23 (s), 158.64 (d), 159.33 (s).

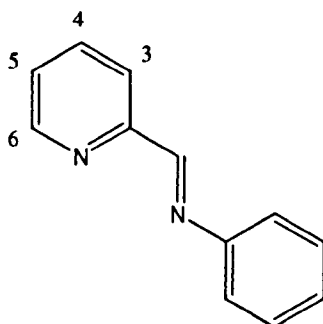
#### 6.2.1.4 Pyridin-2-ylmethylene-(4-trifluoromethyl-phenyl)-amine (64d)



2-pyridinecarboxaldehyde (0.88 ml, 9.33 mmol) and 4-aminobenzotrifluoride (1.17 ml, 9.33 mmol) were reacted as described above (6.2.1) to yield pyridin-2-ylmethylene-(4-trifluoromethyl-phenyl)-amine (**64d**) (2.05 g, 89%) as a yellow oil.

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 2853, 1609, 1463, 1376, 1322, 1165, 1129, 1066, 839, 780;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 7.32 (2H, d, *J* 8.0, aromatic H), 7.40-7.44 (1H, ddd, *J* 7.5, *J* 5.0, *J* 1.0, H-4), 7.67 (2H, d, *J* 8.0, aromatic H), 7.82-7.87 (1H, app dt, *J* 7.5, *J* 1.0, H-5), 8.20 (1H, d, *J* 7.5, H-6), 8.57 (1H, s, *CH=N*), 8.74 (1H, d, *J* 5.0, H-3);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 114.53 (s), 121.52 (2 x d), 122.62 (d), 126.03 (d), 127.05 (2 x d), 137.21 (d), 137.48 (s), 150.28 (d), 150.62 (s), 154.55 (s), 162.87 (d);  $\delta_{\text{F}}$ (282 MHz, CDCl<sub>3</sub>) -62.55 (3F, s, CF<sub>3</sub>); *m/z* (EI) 151 (MH<sup>+</sup>, 22%), 145 (36), 70 (13); (Found: MH<sup>+</sup>, 251.1084. C<sub>13</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub> requires MH<sup>+</sup>, 251.1079).

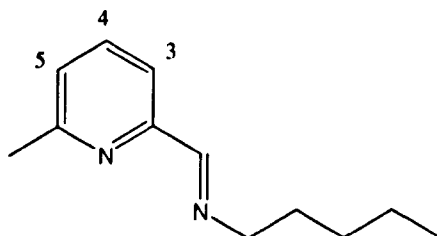
### 6.2.1.5 Phenyl-pyridin-2-ylmethylene-amine (64a)<sup>4</sup>



2-pyridinecarboxaldehyde (0.88 ml, 9.33 mmol) and aniline (0.85 ml, 9.33 mmol) were reacted as described above (6.2.1) to yield phenyl-pyridin-2-ylmethylene-amine (**64a**) (1.56 g, 94%) as a yellow solid. Spectral details match those previously reported.<sup>4</sup>

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 6.64-6.70 (3H, m, aromatic H), 6.74-6.84 (3H, m, 2 x aromatic H and H-4), 7.18-7.23 (1H, app dt,  $J$  7.5,  $J$  1.5, H-5), 7.60 (1H, d,  $J$  8.0, H-6), 8.01 (1H, s,  $\text{CH}=\text{N}$ ), 8.10-8.12 (1H, m, H-3);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 121.51 (2 x d), 122.31 (d), 125.56 (d), 127.14 (d), 129.64 (2 x d), 137.09 (d), 150.12 (d), 151.36 (s), 154.95 (s), 161.04 (d).

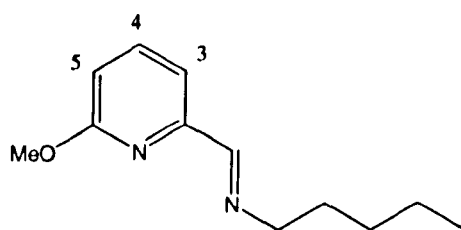
### 6.2.1.6 (6-Methyl-pyridin-2-ylmethylene)-pentylamine (51b)



6-Methyl-2-pyridinecarboxaldehyde (prepared according to standard literature procedures) (2.0g, 16.5 mmol) and *n*-pentylamine (1.9 ml, 16.5 mmol) were reacted as described above (6.2.1) to yield (6-methyl-pyridin-2-ylmethylene)-pentylamine (**51b**) (2.5 g, 82%) as a pale yellow oil which was used without further purification.

$\nu_{\max}$  (film) /cm<sup>-1</sup>: 3060, 2927, 2855, 1648, 1589, 1572, 1455, 1374, 1325, 1036, 791;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 0.91 (3H, t, *J* 7.0, CH<sub>2</sub>CH<sub>3</sub>), 1.29-1.38 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.66-1.78 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.62 (3H, s, CH<sub>3</sub>), 3.68 (2H, dt, *J* 7.0, *J* 1.0, NCH<sub>2</sub>CH<sub>2</sub>), 7.19 (1H, d, *J* 7.0, H-5), 7.63 (1H, t, *J* 7.0, H-4), 7.78 (1H, d, *J* 7.0, H-3), 8.35 (1H, s, CH=N);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 14.37 (q), 22.82 (t), 24.67 (q), 29.85 (t), 30.73 (t), 61.94 (t), 118.58 (d), 124.54 (d), 137.06 (d), 154.45 (s), 158.39 (s), 162.33 (d); *m/z* (EI) 191 (MH<sup>+</sup>, 26%), 149 (100), 133 (85), 71 (42); (Found: MH<sup>+</sup>, 191.1549. C<sub>12</sub>H<sub>18</sub>N<sub>2</sub> requires MH<sup>+</sup>, 191.1550).

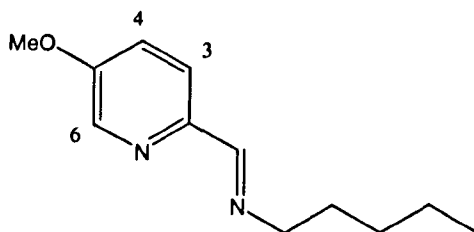
#### 6.2.1.7 (6-Methoxy-pyridin-2-ylmethylene)-pentylamine (**51c**)



6-Methoxy-2-pyridinecarboxaldehyde (synthesised according to standard literature procedures) (0.46g, 3.36 mmol) and *n*-pentylamine (0.39 ml, 3.36 mmol) were reacted as described above (6.2.1) to yield (6-methoxy-pyridin-2-ylmethylene)-pentylamine (**51c**) (0.67g, 89%) as a pale yellow oil which was used without further purification.

$\nu_{\max}$  (film) /cm<sup>-1</sup>; 2928, 2857, 1649, 1595, 1572, 1467, 1433, 1320, 1266, 1032, 804;  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>) 0.89 (3H, t, *J* 7.0, CH<sub>2</sub>CH<sub>3</sub>), 1.31-1.36 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.70 (2H, qn, *J* 7.0, NCH<sub>2</sub>CH<sub>2</sub>), 3.63 (2H, t, *J* 7.0, NCH<sub>2</sub>CH<sub>2</sub>), 3.96 (3H, s, OCH<sub>3</sub>), 6.74 (1H, dd, *J* 7.5, *J* 1.5, H-5), 7.56-7.63 (2H, m, H-3 and H-4), 8.24 (1H, s, CH=N);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 14.43 (q), 22.88 (t), 29.94 (t), 30.85 (t), 53.72 (q), 61.96 (t), 112.27 (d), 114.32 (d), 139.23 (d), 152.67 (s), 162.18 (d), 164.24 (s); *m/z* (EI) 207 (MH<sup>+</sup>, 19%), 149 (85), 135 (60), 71 (47), 57 (71), 41 (83); (Found: MH<sup>+</sup>, 207.1487. C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O requires MH<sup>+</sup>, 207.1498).

#### 6.2.1.8 (5-Methoxy-pyridin-2-ylmethylene)-pentylamine (54d)

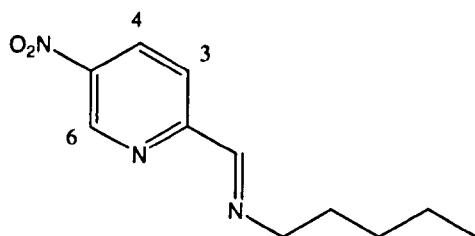


5-Methoxy-2-pyridinecarboxaldehyde (prepared according to standard literature procedures) (46.0 mg, 0.33 mmol) and *n*-pentylamine (0.04 ml, 0.4 mmol) were reacted as described above (6.2.1) to yield (5-methoxy-pyridin-2-ylmethylene)-pentylamine (**54d**) (58 mg, 85%) as a pale yellow oil which was used without further purification.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2954, 2929, 1649, 1589, 1467, 1436, 1331, 1044;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 0.87 (3H, t, *J* 7.0, CH<sub>2</sub>CH<sub>3</sub>), 1.28-1.35 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.65-1.71 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 3.59 (2H, dt, *J* 7.0, *J* 1.0, NCH<sub>2</sub>CH<sub>2</sub>), 3.87 (3H, s, OCH<sub>3</sub>), 7.21 (1H, dd, *J*

8.5, *J* 3.0, H-4), 7.91 (1H, d, *J* 8.5, H-3), 8.27 (1H, s, *CH=N*), 8.29 (1H, s, H-6);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 13.81 (q), 22.26 (t), 29.28 (t), 30.26 (t), 55.46 (q), 61.27 (t), 120.56 (d), 121.69 (d), 136.68 (d), 147.35 (s), 156.34 (s), 160.72 (d); *m/z* (EI) 207 ( $\text{MH}^+$ , 6%), 149 (64), 71 (100); (Found:  $\text{MH}^+$ , 207.1503.  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$  requires  $\text{MH}^+$ , 207.1498).

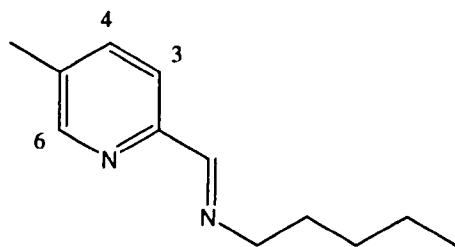
#### 6.2.1.9 (5-Nitro-pyridin-2-ylmethylene)-pentylamine (54c)



5-Nitro-2-pyridinecarboxaldehyde (prepared according to standard literature procedures) (0.5 g, 3.29 mmol) and *n*-pentylamine (0.4 ml, 3.29 mmol) were reacted as described above (6.2.1) to yield (5-nitro-pyridin-2-ylmethylene)-pentylamine (**54c**) (0.61 g, 83%) as a pale yellow oil which was used without further purification.

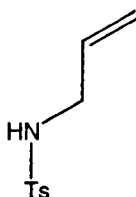
$\nu_{\text{max}}$  (film)  $/\text{cm}^{-1}$  3046, 2955, 2858, 1644, 1597, 1524, 1456, 1351, 1016, 830;  $\delta_{\text{H}}$ (250 MHz,  $\text{CDCl}_3$ ) 0.91 (3H, t, *J* 7.0,  $\text{CH}_2\text{CH}_3$ ), 1.29-1.38 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.68-1.76 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.72 (2H, t, *J* 7.0,  $\text{NCH}_2\text{CH}_2$ ), 8.20 (1H, d, *J* 8.5, H-3), 8.43 (1H, s, *CH=N*), 8.51 (1H, dd, *J* 8.5 *J* 2.5, H-4), 9.44 (1H, d, *J* 2.5, H-6);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 14.40 (q), 22.83 (t), 29.88, (t), 30.62 (t), 62.17 (t), 121.60 (d), 132.01 (d), 144.96 (s), 145.29 (d), 159.61 (s), 160.17 (d); *m/z* (EI) 222 ( $\text{MH}^+$ , 78%), 208 (96), 192 (90), 164 (92), 149 (100); (Found:  $\text{MH}^+$ , 222.1247.  $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2$  requires  $\text{MH}^+$ , 222.1244).

## 6.2.1.10 (5-Methyl-pyridin-2-ylmethylene)-pentylamine (54b)



5-Methyl-2-pyridinecarboxaldehyde (synthesised in accordance to standard literature procedures) (0.85g, 7.0 mmol) and *n*-pentylamine (0.81 ml, 7.0 mmol) were reacted as described above (6.2.1) to yield (5-methyl-pyridin-2-ylmethylene)-pentylamine (**54b**) (0.92g, 71%) as a pale yellow oil which was used without further purification.

$\nu_{\max}$  (film) / $\text{cm}^{-1}$ ; 2929, 2853, 1649, 1569, 1372, 1041, 792;  $\delta_{\text{H}}$ (250 MHz,  $\text{CDCl}_3$ ) 0.87 (3H, t,  $J$  7.0,  $\text{CH}_2\text{CH}_3$ ), 1.30-1.35 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.69 (2H, qn,  $J$  7.0,  $\text{NCH}_2\text{CH}_2$ ), 2.34 (3H, s,  $\text{CH}_3$ ), 3.62 (2H, t,  $J$  7.0,  $\text{NCH}_2\text{CH}_2$ ), 7.51 (1H, dd,  $J$  8.0,  $J$  2.0, H-4), 7.85 (1H, d,  $J$  8.0, H-3), 8.31 (1H, s,  $\text{CH}=\text{N}$ ), 8.44 (1H, d,  $J$  2.0, H-6);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 14.05 (q), 22.50 (t), 24.36 (q), 29.53 (t), 30.49 (t), 61.63 (t), 118.27 (d), 124.25 (d), 136.76 (d), 154.11 (s), 158.08 (s), 162.03 (d);  $m/z$  (EI) 191 ( $\text{MH}^+$ , 63%), 149 (97), 133 (83); (Found:  $\text{MH}^+$ , 191.1547.  $\text{C}_{12}\text{H}_{18}\text{N}_2$  requires  $\text{MH}^+$ , 191.1549).

6.2.2 *N*-Allyl-*N*-toluenesulfonamide (65)<sup>5</sup>

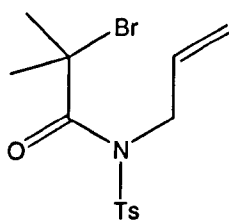
To a stirred solution of tosyl chloride (30.0g, 0.16 mol) in THF (100 ml) was added allylamine (26.4 ml, 0.35 mol) dropwise and the resulting mixture stirred for 2 hours. The mixture was then extracted with dichloromethane (2 x 100 ml) and washed with water (2 x 50 ml), dilute HCl (2 x 50 ml) and a saturated solution of sodium bicarbonate (2 x 50 ml). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to afford *N*-allyl-*N*-toluenesulfonamide (65) (26.54g, 82%) as a white crystalline solid; m.p. 98-100°C (from diethyl ether). Spectral details match those previously reported.<sup>5</sup>

$\nu_{\text{max}}$  (film) /cm<sup>-1</sup> 3460, 2958, 2921, 2854, 1624 $\delta$ ;  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>) 2.48 (3H, s, *CH*<sub>3</sub>), 3.62 (2H, t, *J* 5.0, *CH*<sub>2</sub>CH=CH<sub>2</sub>), 4.45 (1H, br, *NH*), 5.10-5.22 (2H, m, CH=CH<sub>2</sub>), 5.68-5.81 (1H, m, *CH*=CH<sub>2</sub>), 7.34 (2H, d, *J* 8.0, aromatic H), 7.77 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 21.92 (q), 46.12 (t), 117.98 (t), 127.55 (2 x d), 130.12 (2 x d), 133.38 (d), 137.27 (s), 143.87 (s); *m/z* (EI) 212 (MH<sup>+</sup>, 19%), 155 (63), 91 (100).

### 6.2.3 General procedure for the preparation of *N*-allyl-*N*-toluenesulfonyl-*N*-haloacetamides.

To a solution of *N*-allyl-*N*-toluenesulfonamide (**65**) in THF at -78°C under a nitrogen atmosphere was added *n*-BuLi (1.6 M in hexanes, 1.1 eq.) and the resulting solution stirred for 30 mins. The appropriate haloacetyl halide (1.1 eq.) was added and the mixture allowed to stir for 3 hours at -78°C. The reaction was quenched with saturated ammonium chloride solution and allowed to warm to RT. The mixture was extracted with dichloromethane (3 x 50ml) and washed with a saturated solution of sodium bicarbonate (2 x 50ml). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure.

#### 6.2.3.1 *N*-Allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide (**67**)



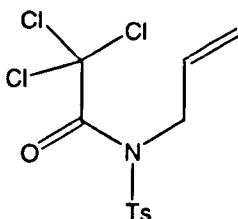
*n*-BuLi (12.5 ml, 1.6M in hexanes) was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (**65**) (4g, 19.0 mmol) in THF (40 ml) then 2-bromo-2-methylpropionyl bromide (2.5 ml, 21.0 mmol) was added. Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent afforded *N*-allyl-*N*-4-



toluenesulfonyl-2-bromo-2-methylpropionamide (**67**) (5.38g, 80%) as a white crystalline solid; m.p. 83-84°C (from hexanes).

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 2921, 1672, 1645, 1592, 1351, 1162, 847;  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>) 1.90 (6H, s, *CH*<sub>3</sub>CBr*CH*<sub>3</sub>), 2.45 (3H, s, *CH*<sub>3</sub>), 4.98 (2H, dt, *J* 5.5, *J* 1.5, *CH*<sub>2</sub>CH=CH<sub>2</sub>), 5.34-5.46 (2H, m, CH=CH<sub>2</sub>), 5.94-6.07 (1H, m, CH=CH<sub>2</sub>), 7.32 (2H, d, *J* 8.0, aromatic H), 7.89 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 22.09 (q), 32.42 (2 x q), 51.01 (t), 57.41 (s), 118.59 (t), 129.26 (2 x d), 129.61 (2 x d), 133.93 (d), 136.48 (s), 145.05 (s), 170.76 (s); *m/z* (EI) 362 [(MH-<sup>81</sup>Br)<sup>+</sup>, 23%], 360 [(MH-<sup>79</sup>Br)<sup>+</sup>, 25%], 295 (100), 280 (68), 155 (54), 91 (100); (Found: MH<sup>+</sup>, 360.0263. C<sub>14</sub>H<sub>18</sub><sup>79</sup>BrNO<sub>3</sub>S requires MH<sup>+</sup>, 360.0269).

#### 6.2.3.2 *N*-Allyl-*N*-toluenesulphonyl-2,2,2-trichloroacetamide (**66**)<sup>6</sup>



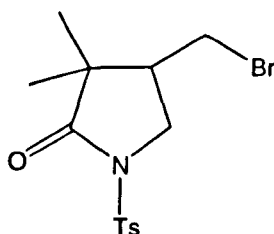
*n*-BuLi (12.5 ml, 1.6M in hexanes) was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (**65**) (4g, 19.0 mmol) in THF (40 ml) then trichloroacetyl chloride (2.23 ml, 21.0 mmol) was added. Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent afforded *N*-allyl-*N*-4-toluenesulfonyl-2,2,2-trichloroacrtamide (**66**) (4.2g, 60%) as a white crystalline solid; m.p. 74-76°C (from hexanes). Spectral details match those previously reported.<sup>6</sup>

$\nu_{\max}$  (nujol) / $\text{cm}^{-1}$  2923, 1712, 1595, 1358, 1167, 840, 813;  $\delta_{\text{H}}$ (250 MHz,  $\text{CDCl}_3$ ) 2.44 (3H, s,  $\text{CH}_3$ ), 4.91 (2H, dt,  $J$  5.5,  $J$  1.5,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.34-5.48 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.89-6.01 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.33 (2H, d,  $J$  8.0, aromatic H), 7.91 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 22.16 (q), 51.50 (t), 98.23 (s), 119.33 (t), 129.84 (2 x d), 129.92 (2 x d), 132.66 (d), 135.10 (s), 146.04 (s), 158.96 (s);  $m/z$  (EI) 356 ( $\text{MH}^+$ , 32%), 291 (100), 211 (52), 155 (80), 91 (51); (Found:  $\text{MH}^+$ , 355.9669.  $\text{C}_{12}\text{H}_{12}\text{Cl}_3\text{NO}_3\text{S}$  requires  $\text{MH}^+$ , 355.9681).

#### 6.2.4 General procedure for the cyclisation of *N*-allyl-*N*-toluenesulfonyl-*N*-haloacetamides.

To a mixture of *N*-allyl-*N*-toluenesulfonyl-*N*-haloacetamide and copper halide (30 mol%) under a nitrogen atmosphere was added a solution of ligand (30 mol%) in dry dichloromethane (0.12M solution). The resulting mixture was stirred at room temperature and upon completion was eluted through a silica plug with dichloromethane. Subsequent removal of solvent under reduced pressure furnished the  $\gamma$ -lactam as a white solid.

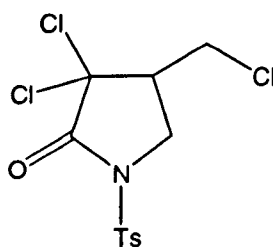
##### 6.2.4.1 4-Bromomethyl-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (68)



*N*-Allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide (**67**) (100 mg, 0.27mmol) was reacted as described above (6.2.5) to furnish 4-bromomethyl-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**68**) (94 mg, 94%) as a white crystalline solid; m.p. 131-133°C.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2923, 1724, 1458, 1375, 1354, 1170, 1090, 815;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 0.91 (3H, s, *CH*<sub>3</sub>CCH<sub>3</sub>), 1.18 (3H, s, CH<sub>3</sub>CCH<sub>3</sub>), 2.45 (3H, s, *CH*<sub>3</sub>), 2.45 (1H, m, *CHCH*<sub>2</sub>Br), 3.22 (1H, t, *J* 10.5, *CHHN*), 3.47 (2H, m, *CH*<sub>2</sub>Br), 4.16 (1H, dd, *J* 10.5, *J* 7.5, *CHHN*), 7.35 (2H, d, *J* 8.0, aromatic H), 7.94 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 16.81 (q), 20.70 (q), 22.42 (q), 28.81 (t), 43.99 (d), 44.39 (s), 47.77 (t), 126.94 (2 x d), 128.72 (2 x d), 133.78 (s), 144.33 (s), 175.87 (s); *m/z* (EI) 360 (MH<sup>+</sup>, 14%), 295 (67), 155 (100), 91 (82); (Found: MH<sup>+</sup>, 360.0264. C<sub>14</sub>H<sub>18</sub>BrNO<sub>3</sub>S requires MH<sup>+</sup>, 360.0270).

#### 6.2.4.2 3,3-Dichloro-4-chloromethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**69**)



*N*-Allyl-*N*-toluenesulphonyl-2,2,2-trichloroacetamide (**66**) (100 mg, 0.28 mmol) was reacted as described above (6.2.5) to furnish 3,3-dichloro-4-chloromethyl-1-(toluene-4-

sulfonyl)-pyrrolidin-2-one (**69**) (97 mg, 97%) as a white crystalline solid; m.p. 156-158 °C.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2922, 2852, 1752, 1462, 1375, 1173, 1088, 813;  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>) 2.36 (3H, s, *CH*<sub>3</sub>), 2.94-3.10 (1H, m, *CHCH*<sub>2</sub>Cl), 3.52 (1H, dd, *J* 10.0, *J* 8.0, *CHHN*), 3.63 (1H, dd, *J* 11.5, *J* 10.0, *CHHCl*), 3.89 (1H, dd, *J* 11.5, *J* 4.0, *CHHCl*), 4.18 (1H, dd, *J* 10.0, *J* 7.0, *CHHN*), 7.31 (2H, d, *J* 8.0, aromatic H), 7.86 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 20.79 (q), 39.15 (t), 46.82 (t), 49.62 (d), 81.63 (s), 127.25 (2 x d), 129.04 (2 x d), 132.28 (s), 145.41 (s), 162.02 (s); *m/z* (EI) 356 (MH<sup>+</sup>, 23%), 155 (100), 91 (68); (Found: MH<sup>+</sup>, 355.9672. C<sub>12</sub>H<sub>12</sub>Cl<sub>3</sub>NO<sub>3</sub>S requires MH<sup>+</sup>, 355.9681).

### 6.3 Experimental for chapter 3.

#### 6.3.1 4-Methyl-*N*-prop-2-ynyl-benzenesulfonamide (**75**)<sup>7</sup>

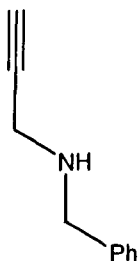


To a stirred solution of tosyl chloride (3.12 g, 16.0 mmol) in dichloromethane (10 ml) was added propargylamine hydrochloride (1.5 g, 16.0 mmol) and triethylamine (4.56 ml, 33.0 mmol), the resulting mixture was then stirred for 2 hours. The mixture was then washed with water (2 x 10 ml), dilute HCl (2 x 10 ml) and a saturated solution of sodium bicarbonate (2 x 20 ml). The organic extracts were then dried over anhydrous magnesium

sulfate and the solvent removed under reduced pressure to afford 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**75**) (2.53g, 75%) as a colourless viscous oil. Spectral details match those previously reported.<sup>7</sup>

$\delta_{\text{H}}$ (250 MHz,  $\text{CDCl}_3$ ) 2.09 (1H, t,  $J$  2.5,  $\text{CCH}$ ), 2.42 (3H, s,  $\text{CH}_3$ ), 3.81 (2H, dd,  $J$  6.0,  $J$  2.5,  $\text{NHCH}_2$ ), 4.57 (1H, br,  $\text{NH}$ ), 7.30 (2H, d,  $J$  8.0, aromatic H), 7.75 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 21.97 (q), 33.27 (t), 73.41 (d), 78.32 (s), 127.79 (2 x d), 130.11 (2 x d), 136.85 (s), 144.28 (s);  $m/z$  (EI) 227 ( $\text{MNH}_4^+$ , 66%), 118 (51), 91 (100); (Found:  $\text{MNH}_4^+$ , 227.0849.  $\text{C}_{10}\text{H}_{11}\text{NO}_2\text{S}$  requires  $\text{MNH}_4^+$ , 227.0854).

### 6.3.2 Benzyl-prop-2-ynyl-amine (**83**)

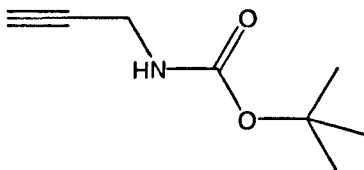


To a stirred solution of propargylamine hydrochloride (3.0 g, 33.0 mmol) in dichloromethane (20 ml) was added benzyl bromide (0.77 ml, 6.6 mmol) and triethylamine (4.6 ml, 33.0 mmol), the resulting mixture was then stirred at room temperature overnight. The mixture was then washed with water (3 x 20 ml) and a saturated solution of sodium bicarbonate (3 x 20 ml). The organic extracts were then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Purification by flash column chromatography using 5:2 petroleum ether:ethyl

acetate as eluent afforded benzyl-prop-2-ynyl-amine (**83**) (0.78 g, 82%) as a colourless viscous oil.

$\nu_{\max}$  (nujol) / $\text{cm}^{-1}$  3226, 2133, 1064, 732, 686;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.17 (1H, br, *NH*), 2.18 (1H, t, *J* 2.0, *CCH*), 3.45 (2H, d, *J* 2.0, *NCH*<sub>2</sub>), 3.91 (2H, s, *NCH*<sub>2</sub>Ph), 7.26-7.37 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 37.71 (t), 52.65 (t), 71.98 (d), 82.42 (s), 127.58 (d), 128.83 (2 x d), 128.85 (2 x d), 139.74 (s); *m/z* (EI) 146 ( $\text{MH}^+$ , 35%), 91 (12); (Found:  $\text{MH}^+$ , 146.0969.  $\text{C}_{10}\text{H}_{11}\text{N}$  requires  $\text{MH}^+$ , 146.0969).

### 6.3.3 Prop-2-ynyl-carbamic acid tert-butyl ester (**80**)



To a solution of propargylamine hydrochloride (1.5 g, 16.0 mmol) and triethyl amine (2.23 ml, 16.0 mmol) in dichloromethane (20 ml.) was added a solution of di *tert*-butyl dicarbonate (3.57 g, 16.0 mmol) in dichloromethane (5.0 ml). The resulting mixture was stirred at room temperature for 2 hours. The solvent was then removed under reduced pressure to yield prop-2-ynyl-carbamic acid tert-butyl ester (**80**) (2.38 g, 96%) as a white solid which was used without further purification.

$\nu_{\max}$  (nujol) / $\text{cm}^{-1}$  3307, 2928, 2136, 1733, 1458, 1373, 1078, 814;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.38 (9H, s, 3 x *CH*<sub>3</sub>), 2.15 (1H, t, *J* 2.5, *CCH*), 3.85 (2H, br d, *J* 2.5, *NHCH*<sub>2</sub>), 4.70 (1H,

br, *NH*);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 28.71 (3 x q), 31.59 (t), 46.19 (s), 71.62 (d), 80.47 (s), 155.64 (s);  $m/z$  (EI) 156 ( $\text{MH}^+$ , 82%), 101 (75), 57 (60), 39 (87).

#### 6.3.4 *N*-But-2-ynyl-4-methyl-benzenesulfonamide (212)



To a solution of but-2-ynylamine hydrochloride (1.0 g, 9.47 mmol) and triethyl amine (2.65 ml, 18.9 mol) in dichloromethane (20 ml) was added a solution of tosyl chloride (1.80 g, 9.47 mmol) in dichloromethane (10 ml). The mixture was stirred overnight at room temperature. The solvent was then removed under reduced pressure and the resultant solid dissolved in diethyl ether. The mixture was washed with water (2 x 20 ml), a 10% aqueous solution of hydrochloric acid (2 x 10 ml) and a saturated aqueous solution of sodium hydrogencarbonate (2 x 10 ml). The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to afford *N*-but-2-ynyl-4-methyl-benzenesulfonamide (**212**) (1.78 g, 84%).

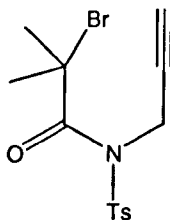
$\nu_{\text{max}}$  (nujol) / $\text{cm}^{-1}$  2256, 2129, 1337, 1145, 1063, 806;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.54 (3H, s,  $\text{CCH}_3$ ), 2.40 (3H, s,  $\text{CH}_3$ ), 3.77 (2H, d,  $J$  6.0,  $\text{NHCH}_2$ ), 4.42 (1H, br, *NH*), 7.27 (2H, d,  $J$  8.0, aromatic H), 7.75 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 1.37 (q), 21.49 (q), 32.64 (t), 77.93 (s), 78.14 (s), 127.77 (2 x d), 130.12 (2 x d), 136.27 (s), 144.49 (s);

$m/z$  (CI) 224 ( $MH^+$ , 49%), 155 (62), 91 (100); (Found:  $MNH_4^+$ , 241.1006.  $C_{11}H_{13}NO_2S$  requires  $MNH_4^+$ , 241.1010).

### 6.3.5 General procedure for the preparation of 1-halo-*N*-propargylacetamides.

To a solution of the protected propargyl amine in THF at  $-78^\circ\text{C}$  under an atmosphere of nitrogen was added *n*-BuLi (1.6 M in hexanes, 1.1 eq.) and the resulting solution stirred for 30 minutes. The appropriate haloacetyl halide (1.1 eq.) was then introduced and the mixture stirred for a further 3 hours at  $-78^\circ\text{C}$ . The reaction was quenched with water and allowed to warm to room temperature. The mixture was then extracted with dichloromethane (3 x 50 ml.) and washed with a saturated aqueous solution of sodium bicarbonate (2 x 50 ml.). The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure.

#### 6.3.5.1 *N*-(2-Bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (76)<sup>8</sup>



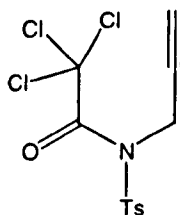
*n*-BuLi (2.98 ml, 1.6M in hexanes) was added to a stirred solution of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (75) (1.0 g, 4.78 mmol) in THF (20 ml) then 2-bromo-2-



methylpropionyl bromide (0.6 ml, 4.78 mmol) was added as described previously (6.3.5). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent afforded *N*-(2-bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl benzenesulfonamide (**76**) (0.93 g, 55%) as a white crystalline solid; m.p. 92-93°C (from hexanes). Spectral details match those previously reported.<sup>8</sup>

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 3296, 2925, 2126, 1691, 1593, 1462, 1353, 1165, 1082, 811;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.97 (6H, s, C(Br)CH<sub>3</sub>CH<sub>3</sub>) 2.45 (3H, s, CH<sub>3</sub>), 2.47 (1H, t, *J* 2.5, CH), 5.15 (2H, d, *J* 2.5, NCH<sub>2</sub>CCH), 7.32 (2H, d, *J* 8.0, aromatic H), 7.99 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 22.12 (q), 32.14 (2 x q), 38.18 (t), 57.12 (s), 77.62 (d), 79.17 (s), 129.48 (2 x d), 129.66 (2 x d), 136.00 (s), 145.35 (s), 170.06 (s); *m/z* (EI) 360 [(MH-<sup>81</sup>Br)<sup>+</sup>, 66%], 358 [(MH-<sup>79</sup>Br)<sup>+</sup>, 67%], 280 (90), 204 (24), 186 (64), 124 (70), 91 (5); (Found: MNH<sub>4</sub><sup>+</sup>, 375.0381. C<sub>14</sub>H<sub>16</sub><sup>79</sup>BrNO<sub>3</sub>S requires MNH<sub>4</sub><sup>+</sup>, 375.0378).

#### 6.3.5.2 4-Methyl-*N*-prop-2-ynyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (**79**)

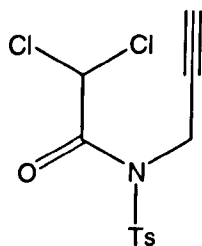


*n*-BuLi (2.98 ml, 1.6M in hexanes) was added to a stirred solution of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**75**) (1.0 g, 4.78 mmol) in THF (20 ml) then trichloroacetyl chloride (0.53 ml, 4.78 mmol) was added as described previously (6.3.5). Purification by

flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent furnished 4-methyl-*N*-prop-2-ynyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (**79**) (1.08 g, 64%) as a white crystalline solid.

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 3279, 2923, 2123, 1717, 1595, 1463, 1358, 1169, 1098, 839;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 2.44 (3H, s, *CH*<sub>3</sub>), 2.45 (1H, t, *J* 2.5, *CH*), 5.06 (2H, d, *J* 2.5, *NCH*<sub>2</sub>CCH), 7.36 (2H, d, *J* 8.0, aromatic H), 8.06 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 22.20 (q), 38.92 (t), 74.47 (d), 78.20 (s), 97.47 (s), 129.86 (2 x d), 130.15 (2 x d), 134.52 (s), 146.33 (s), 164.42 (s); *m/z* (EI) 371 (MNH<sub>4</sub><sup>+</sup>, 96%), 337 (61), 302 (45), 189 (85), 91 (15); (Found: MNH<sub>4</sub><sup>+</sup>, 370.9794. C<sub>12</sub>H<sub>10</sub>Cl<sub>3</sub>NO<sub>3</sub>S requires MNH<sub>4</sub><sup>+</sup>, 370.9791).

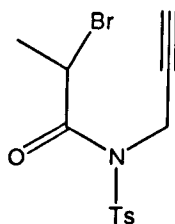
#### 6.3.5.3 *N*-(2,2-Dichloro-acetyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**213**)



*n*-BuLi (2.98 ml, 1.6M in hexanes) was added to a stirred solution of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**75**) (1.0 g, 4.78 mmol) in THF (20 ml) then dichloroacetyl chloride (0.46 ml, 4.78 mmol) was added as described previously (6.3.5). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent furnished *N*-(2,2-dichloro-acetyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**213**) (0.88 g, 58%) as a white crystalline solid.

$\nu_{\max}$  (nujol) / $\text{cm}^{-1}$  3298, 2923, 2853, 1727, 1591, 1462, 1374, 1170, 1102, 851, 656;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 2.30 (1H, t,  $J$  2.5,  $\text{CH}$ ), 2.49 (3H, s,  $\text{CH}_3$ ), 4.67 (2H, d,  $J$  2.5,  $\text{NCH}_2$ ), 6.92 (1H, s,  $\text{ClCHCl}$ ), 7.42 (2H, d,  $J$  8.0, aromatic H), 7.94 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 22.19 (q), 36.69 (t), 63.73 (s), 64.81 (d), 78.03 (s), 128.80 (2 x d), 130.48 (2 x d), 134.81 (s), 146.67 (s), 163.57 (s);  $m/z$  (EI) 337 ( $\text{MNH}_4^+$ , 10%), 255 (6), 227 (15), 155 (63), 91 (100); (Found:  $\text{MNH}_4^+$ , 337.0178.  $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{NO}_3\text{S}$  requires  $\text{MNH}_4^+$ , 337.0180).

#### 6.3.5.4 *N*-(2-Bromo-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (77)

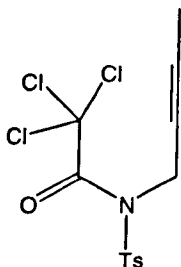


*n*-BuLi (2.98 ml, 1.6M in hexanes) was added to a stirred solution of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (75) (1.0 g, 4.78 mmol) in THF (20 ml) then 2-bromopropionyl bromide (0.5 ml, 4.78 mmol) was added as described previously (6.3.5). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent furnished *N*-(2-bromo-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (77) (1.06 g, 65%) as a colourless oil.

$\nu_{\max}$  (nujol) / $\text{cm}^{-1}$  3262, 2924, 2129, 1696, 1596, 1456, 1159, 1091, 814, 668;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.63 (3H, d,  $J$  6.5,  $\text{CH}_3\text{CHBr}$ ), 2.20 (1H, t,  $J$  2.5,  $\text{CCH}$ ), 2.32 (3H, s,  $\text{CH}_3$ ), 4.49 (1H, dd,  $J$  18.5,  $J$  2.5,  $\text{NCHH}$ ), 4.73 (1H, dd,  $J$  18.5,  $J$  2.5,  $\text{NCHH}$ ), 4.86 (1H, q,  $J$

6.5,  $\text{CH}_3\text{CHBr}$ ), 7.22 (2H, d,  $J$  8.0, aromatic H), 7.79 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 21.48 (q), 22.14 (q), 36.05 (t), 39.63 (d), 68.36 (s), 73.78 (d), 128.74 (2 x d), 130.17 (2 x d), 135.67 (s), 145.89 (s), 169.31 (s);  $m/z$  (EI) 346  $[(\text{MH}^{-81}\text{Br})^+, 36\%]$ , 344  $[(\text{MH}^{-79}\text{Br})^+, 35\%]$ , 281 (45), 174 (85), 155 (80), 91 (100); (Found:  $\text{MNH}_4^+$ , 361.0216.  $\text{C}_{13}\text{H}_{14}^{79}\text{BrNO}_3\text{S}$  requires  $\text{MNH}_4^+$ , 361.0221).

#### 6.3.5.5 *N*-But-2-ynyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (214)

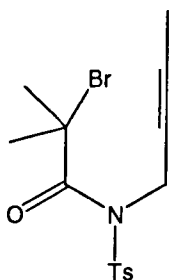


*n*-BuLi (0.43 ml, 1.6M in hexanes) was added to a stirred solution of *N*-but-2-ynyl-4-methyl-benzenesulfonamide (**212**) (0.15 g, 0.67 mmol) in THF (10 ml) then trichloroacetyl chloride (0.075 ml, 0.67 mmol) was added as described previously (6.3.5). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent furnished *N*-but-2-ynyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (**214**) (0.17 g, 72%) as a colourless oil.

$\nu_{\text{max}}$  (nujol)  $/\text{cm}^{-1}$  2923, 2121, 1722, 1598, 1463, 1170, 1081, 837, 648;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.86 (3H, t,  $J$  2.5,  $\text{CCCH}_3$ ), 2.48 (3H, s,  $\text{CH}_3$ ), 5.02 (2H, d,  $J$  2.5,  $\text{NCH}_2$ ), 7.37 (2H, d,  $J$  8.5, aromatic H), 8.08 (2H, d,  $J$  8.5, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 3.99 (q), 22.18 (q), 25.86 (t), 73.74 (s), 82.58 (s), 106.91 (s), 129.71 (2 x d), 130.17 (2 x d),

134.86 (s), 146.13 (s), 163.71 (s);  $m/z$  (CI) 385 ( $\text{MNH}_4^+$ , 62%), 351 (25), 317 (24), 227 (73), 110 (40), 91 (100); (Found:  $\text{MNH}_4^+$ , 384.9991.  $\text{C}_{13}\text{H}_{12}\text{Cl}_3\text{NO}_3\text{S}$  requires  $\text{MNH}_4^+$ , 384.9986).

#### 6.3.5.6 *N*-(2-Bromo-2-methyl-propionyl)-*N*-but-2-ynyl-4-methyl-benzenesulfonamide (95)

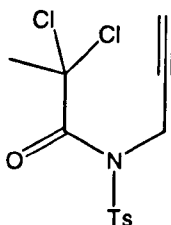


*n*-BuLi (0.42 ml, 1.6M in hexanes) was added to a stirred solution of *N*-but-2-ynyl-4-methyl-benzenesulfonamide (**212**) (0.15 g, 0.67 mmol) in THF (10 ml) then 2-bromo-2-methylpropionyl bromide (0.083 ml, 0.67 mmol) was added as described previously (6.3.5). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent afforded *N*-(2-bromo-2-methyl-propionyl)-*N*-but-2-ynyl-4-methyl-benzenesulfonamide (**95**) (0.16 g, 65%) as a colourless oil.

$\nu_{\text{max}}$  (nujol) / $\text{cm}^{-1}$  2852, 2258, 2126, 1696, 1593, 1463, 1173, 1080, 817, 660;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.86 (3H, t,  $J$  2.5,  $\text{CCCH}_3$ ), 1.98 (6H, s,  $\text{CH}_3\text{C}(\text{Br})\text{CH}_3$ ), 2.45 (3H, s,  $\text{CH}_3$ ), 5.09 (2H, d,  $J$  2.5,  $\text{NCH}_2$ ), 7.33 (2H, d,  $J$  8.5, aromatic H), 8.00 (2H, d,  $J$  8.5, aromatic H);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ) 3.96 (q), 22.09 (q), 30.38 (q), 32.21 (q), 38.87 (t), 57.37 (s), 74.64 (s), 82.28 (s), 129.47 (2 x d), 129.53 (2 x d), 136.30 (s), 145.14 (s), 164.08 (s);  $m/z$

(CI) 391 [( $\text{MNH}_4^+ \text{-}^{81}\text{Br}$ ), 100%], 389 [( $\text{MNH}_4^+ \text{-}^{79}\text{Br}$ ), 98%], 374 [( $\text{MH-}^{81}\text{Br}$ ) $^+$ , 40%], 372 [( $\text{MH-}^{79}\text{Br}$ ) $^+$ , 39%], 294 (26), 217 (40), 140 (45), 91 (100); (Found:  $\text{MNH}_4^+$ , 389.0544.  $\text{C}_{15}\text{H}_{18}^{79}\text{BrNO}_3\text{S}$  requires  $\text{MNH}_4^+$ , 389.0535).

**6.3.5.7      *N*-(2,2-Dichloro-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (78)**

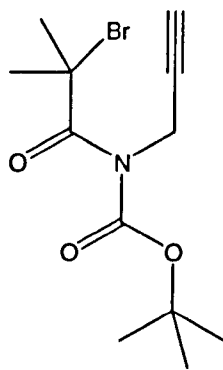


Oxalyl chloride (1.8 ml, 19.0 mmol) was added in a dropwise fashion to 2,2-dichloropropionic acid (1.0 ml, 9.8 mmol) with stirring and the mixture heated under reflux for 2 hours. The excess oxalyl chloride was then removed under reduced pressure to yield 2,2-dichloro-propionyl chloride. This was immediately added to a mixture of *n*-BuLi (3.0 ml, 1.6M in hexanes) and 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**75**) (1.0 g, 4.78 mmol) as described previously (6.3.5). Purification by flash column chromatography using 9:1 petroleum ether:ethyl acetate as eluent afforded *N*-(2,2-dichloro-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**78**) (0.96 g, 66%) as a colourless oil.

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  3291, 3273, 2922, 2126, 1694, 1593, 1367, 1324, 1173, 1080, 823;  
 $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 2.19 (3H, s,  $\text{ClCCH}_3\text{Cl}$ ), 2.44 (1H, t,  $J$  2.5,  $\text{CCH}$ ), 2.46 (3H, s,  $\text{CH}_3$ ), 5.17 (2H, d,  $J$  2.5,  $\text{NCH}_2$ ), 7.33 (2H, d,  $J$  8.0, aromatic H), 8.48 (2H, d,  $J$  8.0,

aromatic H);  $\delta_c$ (75.5 MHz,  $\text{CDCl}_3$ ) 25.93 (q), 35.82 (t), 38.48 (q), 68.35 (d), 78.88 (s), 79.85 (s), 129.73 (2 x d), 129.81 (2 x d), 135.28 (s), 145.81 (s), 163.82 (s);  $m/z$  (CI) 351 ( $\text{MNH}_4^+$ , 65%), 334 ( $\text{MH}^+$ , 4%), 269 (46), 162 (70), 155 (83), 91 (100); (Found:  $\text{MNH}_4^+$ , 351.0339.  $\text{C}_{13}\text{H}_{13}\text{Cl}_2\text{NO}_3\text{S}$  requires  $\text{MNH}_4^+$ , 351.0337).

#### 6.3.5.8 (2-Bromo-2-methyl-propionyl)-prop-2-ynyl-carbamic acid *tert*-butyl ester (81)

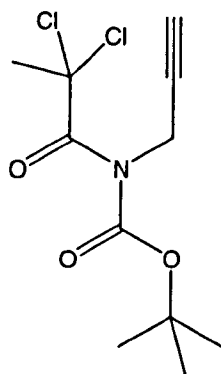


*n*-BuLi (2.66 ml, 1.6M in hexanes) was added to a stirred solution of prop-2-ynyl-carbamic acid *tert*-butyl ester (**80**) (0.6 g, 3.87 mmol) in THF (20 ml) then 2-bromo-2-methylpropionyl bromide (0.53 ml, 4.20 mmol) was added as described previously (6.3.5). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent afforded (2-bromo-2-methyl-propionyl)-prop-2-ynyl-carbamic acid *tert*-butyl ester (**81**) (0.89 g, 76%) as a colourless oil.

$\nu_{\text{max}}$  (nujol) / $\text{cm}^{-1}$  3295, 2936, 1724, 1691, 1592, 1485, 1148, 1072, 811, 781;  $\delta_H$ (300 MHz,  $\text{CDCl}_3$ ) 1.49 (9H, s, 3 x  $\text{CH}_3$ ), 2.02 (6H, s,  $\text{CH}_3\text{C}(\text{Br})\text{CH}_3$ ), 2.16 (1H, t,  $J$  2.5,  $\text{CCH}$ ), 4.30 (2H, d,  $J$  2.5,  $\text{NCH}_2$ ),  $\delta_c$ (75.5 MHz,  $\text{CDCl}_3$ ) 28.28 (3 x q), 33.37 (2 x q), 37.62 (t), 61.57 (s), 66.27 (s), 71.78 (d), 79.16 (s), 152.41 (s), 176.75 (s);  $m/z$  (CI) 306

$[(MH^+ - ^{81}Br), 15\%]$ , 304  $[(MH^+ - ^{79}Br), 15\%]$ , 248 (56), 206 (42), 124 (60), 57 (100);  
(Found:  $MH^+$ , 304.0551.  $C_{12}H_{18}^{79}BrNO_3$  requires  $MH^+$ , 304.0549).

#### 6.3.5.9 (2,2-Dichloro-propionyl)-prop-2-ynyl-carbamic acid *tert*-butyl ester (82)



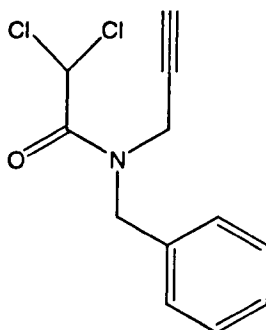
Oxalyl chloride (1.8 ml, 19.0 mmol) was added in a dropwise fashion to 2,2-dichloropropionic acid (1.0 ml, 9.8 mmol) with stirring and the mixture heated under reflux for 2 hours. The excess oxalyl chloride was then removed under reduced pressure to yield 2,2-dichloro-propionyl chloride. This was immediately added to a mixture of *n*-BuLi (1.12 ml, 1.6M in hexanes) and prop-2-ynyl-carbamic acid *tert*-butyl ester (**80**) (0.5 g, 1.79 mmol) as described previously (6.3.5). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent furnished (2,2-dichloro-propionyl)-prop-2-ynyl-carbamic acid *tert*-butyl ester (**82**) (0.12 g, 24%) as a pale yellow oil.

$\nu_{max}$  (nujol) / $cm^{-1}$  3291, 2924, 1695, 1604, 1467, 1369, 1233, 1079, 988, 781;  $\delta_H$ (300 MHz,  $CDCl_3$ ) 1.52 (9H, s, 3 x  $CH_3$ ), 2.20 (1H, t,  $J$  2.5,  $CCH$ ), 2.33 (3H, s,  $ClCCH_3Cl$ ), 4.41 (2H, d,  $J$  2.5,  $NCH_2$ );  $\delta_C$ (75.5 MHz,  $CDCl_3$ ) 28.16 (3 x q), 37.24 (q), 37.95 (t), 72.31



(d), 78.41 (s), 82.24 (s), 85.79 (s), 151.63 (s), 169.15 (s);  $m/z$  (CI) 297 ( $\text{MNH}_4^+$ , 7%), 263 (7), 226 (6), 220 (40), 197 (20), 112 (100); (Found:  $\text{MH}^+$ , 280.0512.  $\text{C}_{11}\text{H}_{15}\text{Cl}_2\text{NO}_3$  requires  $\text{MH}^+$ , 280.0509).

### 6.3.6 *N*-Benzyl-2,2,dichloro-*N*-prop-2-ynyl-acetamide (74)



To a mixture of benzyl-prop-2-ynyl-amine (**83**) (150 mg, 1.03 mmol) and triethyl amine (0.16 ml, 1.14 mmol) in dichloromethane (5 ml.) was added dichloroacetyl chloride (0.11 ml, 1.14 mmol) dropwise. The mixture was stirred for 4 hours at room temperature and then added, with stirring, to a saturated aqueous solution of potassium carbonate (10 ml.). The mixture was extracted with ether (3 x 10 ml.). The combined extracts were then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent furnished *N*-benzyl-2,2,dichloro-*N*-prop-2-ynyl-acetamide (**74**) (160 mg, 62%) as an inseparable mixture of rotomers (ratio 1:1) in the form of a colourless oil.

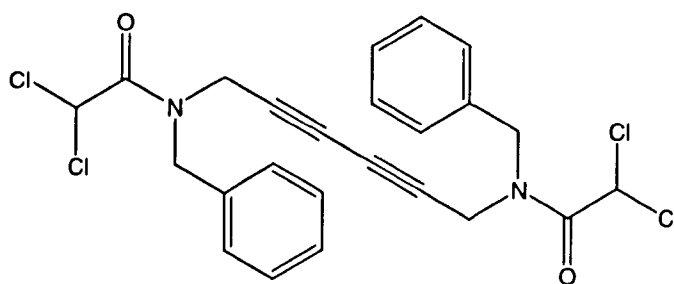
$\nu_{\text{max}}$  (nujol)  $\text{cm}^{-1}$  mixture 3263, 2924, 1697, 1456, 1329, 1159, 1068, 871, 703, 668;  
 $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 2.19 (1/2H, t,  $J$  2.5,  $\text{CCH}$ ), 2.33 (1/2H, t,  $J$  2.5,  $\text{CCH}$ ), 4.08 (1H, d,

$J$  2.5,  $NCH_2$ ), 4.11 (1H, d,  $J$  2.5,  $NCH_2$ ), 4.68 (1H, s,  $NCH_2Ph$ ), 4.77 (1H, s,  $NCH_2Ph$ ), 6.19 (1/2H, s,  $ClCHCl$ ), 6.30 (1/2H, s,  $ClCHCl$ ), 7.15-7.34 (5H, m, aromatic H);  $\delta_C$ (75.5 MHz,  $CDCl_3$ ) *mixture* 35.92 (t), 36.98 (t), 49.73 (t), 50.91 (t), 65.36 (d), 65.61 (d), 73.55 (s), 74.52 (s), 77.62 (d), 77.89 (d), 127.41 (2 x d), 128.45 (d), 128.67 (2 x d), 128.77 (d), 129.29 (2 x d), 129.55 (2 x d), 134.97 (s), 135.67 (s), 163.91 (s), 164.13 (s);  $m/z$  (EI) 256 ( $MH^+$ , 26%), 216 (64), 106 (36), 91 (100).

### 6.3.7 General procedure for the cyclisation of 1-halo-*N*-propargylacetamides.

To a mixture of 1-halo-*N*-propargylacetamide and copper halide (30 mol%) under a nitrogen atmosphere was added a solution of pentylpyridin-2-ylmethyleneamine (**54a**) (30 mol%) in dry dichloromethane (0.12M solution). The resulting mixture was stirred at room temperature overnight and upon completion was eluted through a silica plug with dichloromethane. Subsequent removal of solvent under reduced pressure furnished the corresponding  $\gamma$ -lactam.

#### 6.3.7.1 Cyclisation of *N*-Benzyl-2,2-dichloro-*N*-prop-2-ynyl-acetamide (**74**)

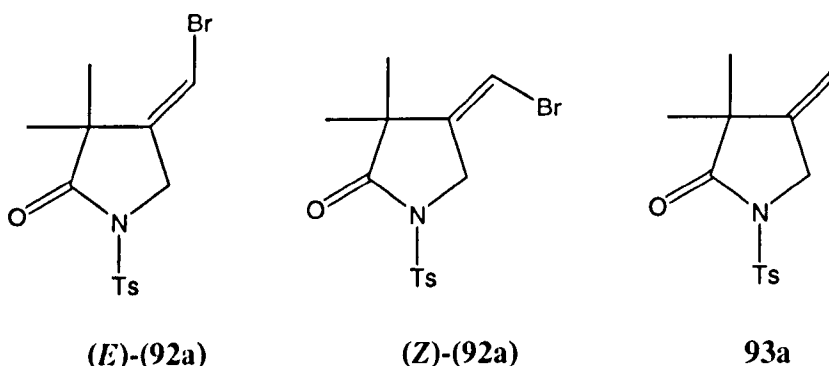


85

N-Benzyl-2,2-dichloro-N-prop-2-ynyl-acetamide (**74**) (40 mg, 0.15 mmol) was reacted as described above (6.3.7) and resulted in the formation of *N*-benzyl-*N*-{6-[benzyl-(2,2-dichloro-acetyl)-amino]-hexa-2,4-diynyl}-2,2-dichloro-acetamide (**85**) (39 mg, 98%) in the form of a colourless oil.

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 2922, 2855, 1698, 1456, 1304, 1159, 1091, 871, 703;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 4.20 (4H, m, 2 x NCH<sub>2</sub>Ph), 4.66 (2H, s, NCH<sub>2</sub>), 4.78 (2H, s, NCH<sub>2</sub>), 6.18 (1H, s, ClCHCl), 6.23 (1H, s, ClCHCl), 7.19-7.34 (10H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 35.05 (t), 36.21 (t), 48.42 (t), 49.83 (t), 63.87 (d), 64.31 (d), 65.35 (2 x s), 73.33 (s), 73.87 (s), 126.05 (2 x d), 126.86 (d), 127.27 (2 x d), 127.50 (d), 127.95 (2 x d), 128.21 (2 x d), 137.32 (s), 137.97 (s), 156.65 (s), 162.67 (s);  $m/z$  (CI) 528 (MNH<sub>4</sub><sup>+</sup>, 92%), 441 (25), 403 (23), 371 (54), 235 (76), 106 (100), 91 (30); (Found: MH<sup>+</sup>, 511.0327. C<sub>24</sub>H<sub>20</sub>Cl<sub>4</sub>N<sub>2</sub>O<sub>2</sub> requires MH<sup>+</sup>, 511.0332).

### 6.3.7.2 Cyclisation of *N*-(2-Bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**76**)



*N*-(2-Bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**76**) (100 mg, 0.28 mmol) was reacted as described above (6.3.7) to yield a mixture of

products (yield of combined products: 96 mgs, 96%). Following purification by flash column chromatography eluting with 4:1 petroleum ether:ethyl acetate (*E*)-4-bromomethyl-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**92a**), (*Z*)-4-bromomethyl-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**92a**) and 3,3-dimethyl-4-methylene-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**93a**) were isolated.

#### 6.3.7.2.1 (*E*)-4-Bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**92a**)<sup>8</sup>

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 2933, 1740, 1672, 1365, 1169, 1046;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.36 (6H, s, CCH<sub>3</sub>CH<sub>3</sub>), 2.39 (3H, s, CH<sub>3</sub>), 4.34 (2H, d, *J* 2.5, NCH<sub>2</sub>), 6.12 (1H, t, *J* 2.5, C=CH(Br)), 7.28 (2H, d, *J* 8.0, aromatic H), 7.88 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 22.13 (q), 22.29 (2 x q), 47.86 (s), 50.50 (t), 101.73 (d), 128.49 (2 x d), 130.19 (2 x d), 135.01 (s), 139.46 (s), 145.99 (s), 176.87 (s); *m/z* (EI) 360 [(MH-<sup>81</sup>Br)<sup>+</sup>, 44%], 358 [(MH-<sup>79</sup>Br)<sup>+</sup>, 44%], 280 (12), 204 (35), 126 (48), 91 (100); (Found: MH<sup>+</sup>, 358.0118. C<sub>14</sub>H<sub>16</sub><sup>79</sup>BrNO<sub>3</sub>S requires MH<sup>+</sup>, 358.0113).

#### 6.3.7.2.2 (*Z*)-4-Bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**92a**)<sup>8</sup>

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 2933, 1740, 1672, 1365, 1169, 1046;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.17 (6H, s, CCH<sub>3</sub>CH<sub>3</sub>), 2.39 (3H, s, CH<sub>3</sub>), 4.38 (2H, d, *J* 2.5, NCH<sub>2</sub>), 6.08 (1H, t, *J* 2.5, C=CH(Br)), 7.28 (2H, d, *J* 8.0, aromatic H), 7.88 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>)

22.13 (q), 25.52 (2 x q), 48.04 (s), 50.32 (t), 102.78 (d), 128.46 (2 x d), 130.21 (2 x d), 135.12 (s), 143.04 (s), 145.96 (s), 176.30 (s);  $m/z$  (EI) 360 [(MH- $^{81}\text{Br}$ ) $^+$ , 56%], 358 [(MH- $^{79}\text{Br}$ ) $^+$ , 57%], 280 (24), 204 (44), 126 (75), 91 (5); (Found: MH $^+$ , 358.0125.  $\text{C}_{14}\text{H}_{16}^{79}\text{BrNO}_3\text{S}$  requires MH $^+$ , 358.0113).

#### 6.3.7.2.3 3,3-Dimethyl-4-methylene-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (93a)<sup>8</sup>

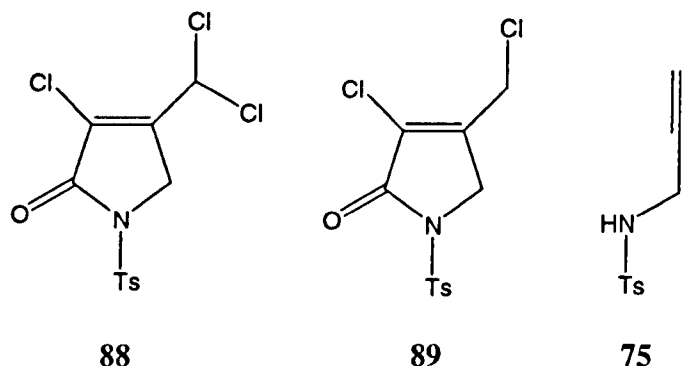
$\nu_{\text{max}}$  (nujol) / $\text{cm}^{-1}$  1731, 1667, 1595, 1463, 1362, 1169, 1122, 901, 814;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.16 (6H, s,  $\text{CCH}_3\text{CH}_3$ ), 2.36 (3H, s,  $\text{CH}_3$ ), 4.37 (2H, t,  $J$  2.0,  $\text{NCH}_2$ ), 5.01 (2H, dt,  $J$  11.5,  $J$  2.0,  $\text{C}=\text{CH}_2$ ), 7.26 (2H, d,  $J$  8.0, aromatic H), 7.84 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 22.12 (q), 24.79 (2 x q), 46.50 (s), 50.32 (t), 108.86 (t), 128.38 (2 x d), 130.11 (2 x d), 135.35 (s), 145.61 (s), 145.68 (s), 177.26 (s);  $m/z$  (EI) 280 (MH $^+$ , 43%), 155 (18), 91 (100); (Found: MH $^+$ , 280.1005.  $\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S}$  requires MH $^+$ , 280.0996).

**Table 14** Results of cyclisation of *N*-(2-Bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (76)

Substrate	Ligand	Solvent	AT:Reduction <sup>a</sup>	Atom trans. <i>E:Z</i>
(76)	NPMI (2)	$\text{CH}_2\text{Cl}_2$	25:1 (96)	5:2
(76)	NPMI (2)	$\text{C}_6\text{H}_6$	74:1 (94)	4:1
(76)	$\text{Me}_6\text{-tren}$	THF	1:20 (95)	4:1
(81)	NPMI (2)	$\text{CH}_2\text{Cl}_2$	10:1 (96)	2:1

<sup>a</sup> Percentage yield of combined products.

### 6.3.7.3 Cyclisation of 4-Methyl-*N*-prop-2-ynyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (79)



4-Methyl-*N*-prop-2-ynyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (79) (100 mg, 0.28 mmol) was reacted as described above (6.3.7) to yield a mixture of products (yield of combined products: 96%). Following purification by flash column chromatography eluting with 4:1 petroleum ether:ethyl acetate, 3-chloro-4-dichloromethyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (88), 3-chloro-4-chloromethyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (89) and 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (75) were isolated.

#### 6.3.7.3.1 3-Chloro-4-dichloromethyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (88)

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  2923, 2855, 1748, 1691, 1652, 1351, 1163, 833;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 2.37 (3H, s,  $\text{CH}_3$ ), 4.65 (2H, s,  $\text{NCH}_2$ ), 6.64 (1H, s,  $\text{ClCHCl}$ ), 7.31 (2H, d,  $J$  8.0, aromatic H), 7.93 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 22.17 (q), 48.12 (t), 62.50 (d), 124.81 (s), 128.72 (2 x d), 130.32 (2 x d), 134.61 (s), 146.54 (s), 147.94 (s), 164.14 (s);

$m/z$  (EI) 371 ( $\text{MNH}_4^+$ , 52%), 354 ( $\text{MH}^+$ , 15%), 337 (30), 303 (36), 189 (52), 155 (12), 91 (12); (Found:  $\text{MH}^+$ , 353.9530.  $\text{C}_{12}\text{H}_{10}\text{Cl}_3\text{NO}_3\text{S}$  requires  $\text{MH}^+$ , 353.9526).

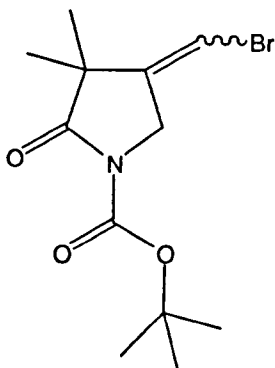
#### 6.3.7.3.2 3-Chloro-4-chloromethyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (89)

$\nu_{\text{max}}$  (neat)  $/\text{cm}^{-1}$  2922, 2851, 1696, 1462, 1343, 1173, 1080, 817;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 2.48 (3H, s,  $\text{CH}_3$ ), 4.39 (2H, s,  $\text{NCH}_2$ ), 4.57 (2H, s,  $\text{CH}_2\text{Cl}$ ), 7.32 (2H, d,  $J$  8.0, aromatic H), 7.98 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 22.14 (q), 36.77 (t), 50.76 (t), 127.79 (s), 128.76 (2 x d), 130.12 (2 x d), 136.47 (s), 146.29 (s), 147.98 (s), 164.17 (s);  $m/z$  (CI) 337 ( $\text{MNH}_4^+$ , 23%), 283 (38), 226 (21), 155 (34), 91 (64).

#### 6.3.7.3.3 4-Methyl-N-prop-2-ynyl-benzenesulfonamide (75)<sup>7</sup>

Isolated as a white crystalline solid, spectral details match those previously cited (section 6.3.1).

**6.3.7.4 4-Bromomethylene-3,3-dimethyl-2-oxo-pyrrolidine-1-carboxylic acid  
*tert*-butyl ester (92b)**

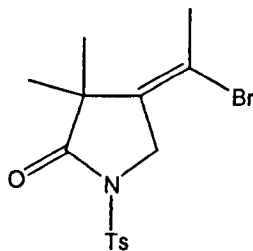


(2-Bromo-2-methyl-propionyl)-prop-2-ynyl-carbamic acid *tert*-butyl ester (**81**) (100 mg, 0.33 mmol) was reacted as described above (6.3.7) to yield 4-bromomethylene-3,3-dimethyl-2-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**92b**) (96 mg, 96%) as an inseparable oily mixture of E/Z isomers (ratio 1:2).

$\nu_{\max}$  (neat) /cm<sup>-1</sup> mixture 2924, 2851, 1772, 1457, 1328, 1296, 1027, 780;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) *major isomer* 1.26 (6H, s, CH<sub>3</sub>CCH<sub>3</sub>), 1.49 (9H, s, 3 x CH<sub>3</sub>), 4.22 (2H, d, *J* 4.5, NCH<sub>2</sub>), 6.08 (1H, t, *J* 4.5, C=CHBr); *minor isomer* 1.44 (6H, s, CH<sub>3</sub>CCH<sub>3</sub>), 1.49 (9H, s, 3 x CH<sub>3</sub>), 4.19 (2H, d, *J* 2.0, NCH<sub>2</sub>), 6.11 (1H, t, *J* 2.0, C=CHBr);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) mixture 21.97 (2 x q), 25.35 (2 x q), 27.78 (3 x q), 47.50 (s), 49.38 (t), 49.66 (t), 83.39 (s), 100.10 (d), 101.27 (d), 139.90 (s), 143.36 (s), 149.58 (s), 176.52 (s); *m/z* (EI) 306 [(MH-<sup>81</sup>Br)<sup>+</sup>, 53%], 304 [(MH-<sup>79</sup>Br)<sup>+</sup>, 56%], 223 (78), 148 (17), 112 (9); (Found: MH<sup>+</sup>, 304.0550 C<sub>12</sub>H<sub>18</sub><sup>79</sup>BrNO<sub>3</sub> requires MH<sup>+</sup>, 304.0548).



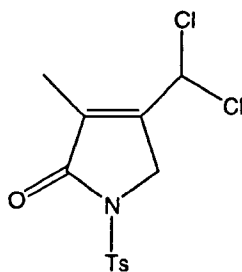
**6.3.7.5      4-(1-Bromo-ethylidene)-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (96)**



*N*-(2-Bromo-2-methyl-propionyl)-*N*-but-2-ynyl-4-methyl-benzenesulfonamide (**95**) (50 mg, 0.13 mmol) was reacted as described above (6.3.7) to yield 4-(1-bromo-ethylidene)-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**96**) (47 mg, 94%) as an inseparable oily mixture of *E/Z* isomers (ratio 1:1).

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 1739, 1669, 1598, 1367, 1178, 1102, 814, 756;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.26 (3H, s, *CH*<sub>3</sub>*CCH*<sub>3</sub>), 1.32 (3H, s, *CH*<sub>3</sub>*CCH*<sub>3</sub>), 2.17 (3/2H, s, C=C(Br)*CH*<sub>3</sub>), 2.34 (3/2H, s, C=C(Br)*CH*<sub>3</sub>), 2.39 (3H, s, *CH*<sub>3</sub>), 4.28 (1H, s, *NCH*<sub>2</sub>), 4.33 (1H, s, *NCH*<sub>2</sub>), 7.27 (2H, d, *J* 8.0, aromatic H), 7.89 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) *mixture* 22.13 (q), 22.66 (q), 24.29 (q), 25.56 (q), 26.62 (q), 47.47 (s), 49.76 (t), 52.47 (t), 119.35 (s), 128.49 (2 x d), 130.16 (2 x d), 134.41 (s), 135.18 (s), 145.87 (s), 177.19 (s); *m/z* (EI) 391 [(MNH<sub>4</sub>-<sup>81</sup>Br)<sup>+</sup>, 22%], 389 [(MNH<sub>4</sub>-<sup>79</sup>Br)<sup>+</sup>, 20%], 374 [(MH-<sup>81</sup>Br)<sup>+</sup>, 25%], 372 [(MH-<sup>79</sup>Br)<sup>+</sup>, 23%], 292 (95), 228 (48), 155 (45), 91 (100); (Found: MH<sup>+</sup>, 372.0263. C<sub>15</sub>H<sub>18</sub><sup>79</sup>BrNO<sub>3</sub>S requires MH<sup>+</sup>, 372.0270).

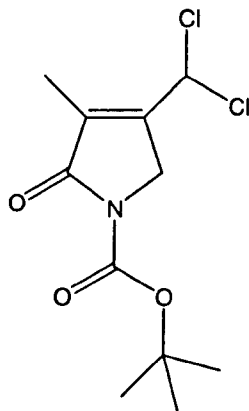
**6.3.7.6 4-Dichloromethyl-3-methyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (86a)**



*N*-(2,2-Dichloro-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**78**) (100 mg, 0.31 mmol) in the presence of CuCl (31 mg, 1 eq.) and pentylpyridin-2-ylmethyleamine (**54a**) (55 mg, 1 eq.) was reacted as previously described (6.3.7). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent afforded 4-dichloromethyl-3-methyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (**86a**) (40 mg, 48%) in the form of a colourless oil.

$\nu_{\max}$  (neat) /cm<sup>-1</sup> 2924, 1736, 1667, 1464, 1363, 1179, 814, 734;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.85 (3H, s, C=CCH<sub>3</sub>), 2.44 (3H, s, CH<sub>3</sub>), 4.64 (2H, s, NCH<sub>2</sub>), 6.65 (1H, s, ClCHCl), 7.37 (2H, d, *J* 8.0, aromatic H), 7.98 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 9.34 (q), 22.12 (q), 48.56 (t), 63.88 (d), 128.55 (2 x d), 130.27 (2 x d), 131.06 (s), 135.34 (s), 145.93 (s), 148.45 (s), 168.04 (s); *m/z* (CI) 334 (MH<sup>+</sup>, 17%), 298 (23), 261 (21), 155 (59), 91 (84); (Found: MH<sup>+</sup>, 334.0065. C<sub>13</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>3</sub>S requires MH<sup>+</sup>, 334.0071).

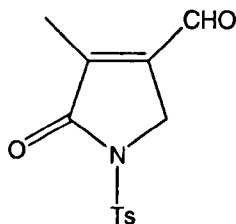
**6.3.7.7      4-Dichloromethyl-3-methyl-2-oxo-2,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester (86b)**



(2,2-Dichloro-propionyl)-prop-2-ynyl-carbamic acid *tert*-butyl ester (**82**) (50 mg, 0.18 mmol) was reacted as previously described (6.3.7). Purification by flash column chromatography using 4:1 petroleum ether:ethyl acetate as eluent afforded 4-dichloromethyl-3-methyl-2-oxo-2,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester (**86b**) (25 mg, 50%) as a colourless oil.

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  2924, 2852, 1775, 1456, 1298, 1155, 1028, 732, 669;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.57 (9H, s, 3 x  $\text{CH}_3$ ), 2.33 (3H, s,  $\text{C}=\text{CCH}_3$ ), 4.41 (2H, s,  $\text{NCH}_2$ ), 6.63 (1H, s,  $\text{ClCHCl}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 9.34 (q), 28.18 (3 x q), 35.01 (t), 64.21 (d), 82.25 (s), 131.44 (s), 147.13 (s), 149.71 (s), 164.23 (s);  $m/z$  (CI) 280 ( $\text{MH}^+$ , 38%), 209 (32), 168 (63), 74 (46).

**6.3.8 4-Methyl-5-oxo-1-(toluene-4-sulfonyl)-2,5-dihydro-1H-pyrrole-3-carbaldehyde (87a)**



To 4-dichloromethyl-3-methyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (**86a**) (13 mg, 0.039 mmol) in 1:1 THF/H<sub>2</sub>O (0.5 ml) was added silver nitrate (28 mg, 0.15 mmol). The mixture was heated under reflux overnight and then extracted with diethyl ether (3 x 1.0 ml). The combined extracts were then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Purification by flash column chromatography eluting with 5:2 petroleum ether:ethyl acetate afforded 4-methyl-5-oxo-1-(toluene-4-sulfonyl)-2,5-dihydro-1H-pyrrole-3-carbaldehyde (**87a**) (10 mg, 77%) as a yellow oil.

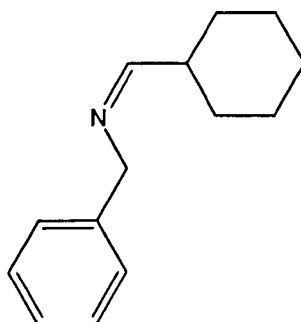
$\nu_{\max}$  (neat) /cm<sup>-1</sup> 2922, 2835, 1774, 1728, 1462, 1367, 1178, 1027, 817;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 2.11 (3H, s, C=CC<sub>3</sub>H<sub>3</sub>), 2.37 (3H, s, CH<sub>3</sub>), 4.44 (2H, s, NCH<sub>2</sub>), 7.28 (2H, d, *J* 8.0, aromatic H), 7.89 (2H, d, *J* 8.0, aromatic H), 10.11 (1H, s, CHO);  $\delta_{\text{C}}$ (100 MHz, CDCl<sub>3</sub>) 9.24 (q), 21.75 (q), 48.41 (t), 128.20 (2 x d), 129.93 (2 x d), 134.79 (s), 144.36 (s), 144.67 (s), 145.71 (s), 168.42 (s), 186.10 (d); *m/z* (EI) 280 (MH<sup>+</sup>, 64%), 250 (7), 155 (82), 91 (100); (Found: MII<sup>+</sup>, 280.0645. C<sub>13</sub>H<sub>13</sub>NO<sub>4</sub>S requires MH<sup>+</sup>, 280.0644).

## 6.4 Experimental for chapter 4

### 6.4.1 General procedure for preparation of methylene-amines

To a stirred solution of the aldehyde in dry dichloromethane containing anhydrous magnesium sulfate under a nitrogen atmosphere was added primary amine (1 eq.). The resulting mixture was stirred for four hours at room temperature. The magnesium sulfate was removed by filtration and the solvent removed under reduced pressure to afford the imine.

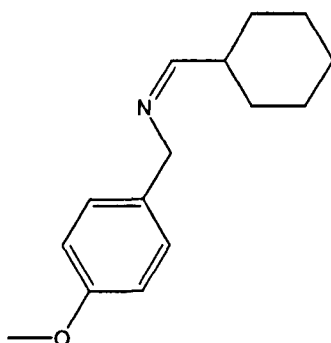
#### 6.4.1.1 Benzyl-cyclohexylmethylene-amine (215)<sup>9</sup>



Cyclohexanecarboxaldehyde (2.25 ml, 18.6 mmol) and benzylamine (2.04 ml, 18.6 mmol) were reacted as described above (6.4.1) to afford benzyl-cyclohexylmethylene-amine (**215**) (3.1g, 87%) as a colourless oil which was used without further purification. Spectral details match those previously reported.<sup>9</sup>

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.1-1.32 (5H, m,  $\text{CH}_2$ ), 1.57-1.79 (5H, m,  $\text{CH}_2$ ), 2.12-2.22 (1H, m,  $\text{NCHCH}$ ), 4.47 (2H, s,  $\text{NCH}_2\text{Ph}$ ), 7.13-7.27 (5H, m, aromatic H), 7.56 (1H, d,  $J$  5.0,  $\text{N=CH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 25.87 (2 x t), 26.41 (t), 30.11 (2 x t), 43.98 (d), 65.38 (t), 127.20 (d), 128.17 (2 x d), 128.80 (2 x d), 139.91 (s), 170.64 (d);  $m/z$  (EI) 202 ( $\text{MH}^+$ , 18%), 146 (58), 133 (94), 91 (100);

#### 6.4.1.2 Cyclohexylmethylene-(4-methoxy-benzyl)-amine (216)

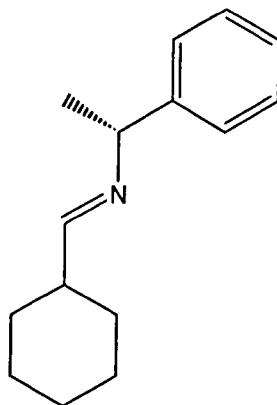


Cyclohexanecarboxaldehyde (2.25 ml, 18.6 mmol) and *p*-methoxy-benzylamine (2.4 ml, 18.6 mmol) were reacted as described above (6.4.1) to yield cyclohexylmethylene-(4-methoxy-benzyl)-amine (**216**) (3.98g, 92%) as a colourless oil which was used without further purification.

$\nu_{\text{max}}$  (film)  $/\text{cm}^{-1}$  3313, 2924, 1666, 1610, 1512, 1446, 1247, 1174, 1034, 820;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.13-1.29 (5H, m,  $\text{CH}_2$ ), 1.57-1.77 (5H, m,  $\text{CH}_2$ ), 2.1-2.23 (1H, m,  $\text{NCHCH}$ ), 3.76 (3H, s,  $\text{OCH}_3$ ), 4.41 (2H, s,  $\text{NCH}_2\text{Ar}$ ), 6.79 (2H, d,  $J$  9.5, aromatic H), 7.08 (2H, d,  $J$  9.5, aromatic H), 7.54 (1H, d,  $J$  5.0,  $\text{N=CH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 25.85

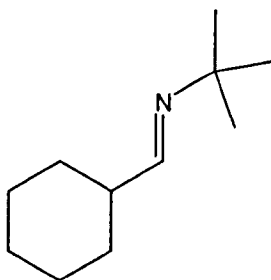
(2 x t), 26.4 (t), 30.11 (2 x t), 43.94 (d), 55.63 (q), 64.81 (t), 114.2 (2 x d), 130.19 (2 x d), 132.03 (s), 158.92 (s), 170.21 (d);  $m/z$  (EI) 232 ( $MH^+$ , 7%), 163 (37), 121 (100), 91 (44);

#### 6.4.1.3 Cyclohexylmethylene-(1-phenyl-ethyl)-amine (**217**)<sup>10</sup>



Cyclohexanecarboxaldehyde (2.0 ml, 15.5 mmol) and (*R*)-(+)-methylbenzylamine (1.87 ml, 15.5 mmol) were reacted as described above (6.4.1) to yield cyclohexylmethylene-(1-phenyl-ethyl)-amine (**217**) (3.23g, 96%) which was obtained as a colourless oil and was used without further purification. Spectral details match those previously reported.<sup>10</sup>

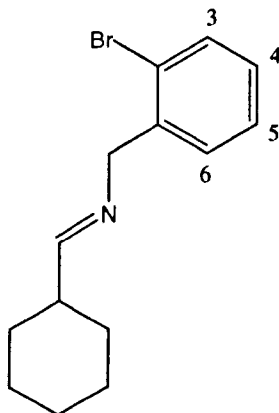
$\delta_H$ (300 MHz,  $CDCl_3$ ) 1.08-1.33 (5H, m,  $CH_2$ ), 1.4 (3H, d,  $J$  7.0,  $CH_3$ ), 1.55-1.78 (5H, m,  $CH_2$ ), 2.09-2.19 (1H, m,  $N=CHCH$ ), 4.17 (1H, q,  $J$  7.0,  $NCH(CH_3)Ph$ ), 7.11-7.28 (5H, m, aromatic H), 7.51 (1H, d,  $J$  5.5,  $N=CH$ );  $\delta_C$ (75.5 MHz,  $CDCl_3$ ) 25.13 (q), 25.78 (2 x t), 26.36 (t), 30.17 (2 x t), 43.90 (d), 69.88 (d), 126.87 (2 x d), 127.05 (d), 128.73 (2 x d), 145.64 (s), 168.12 (d);  $m/z$  (EI) 232 ( $MNH_3^+$ , 96%), 216 ( $MH^+$ , 85), 150 (100), 105 (55), 91 (23).

6.4.1.4 *tert*-Butyl-cyclohexylmethylene-amine (218)<sup>11</sup>

Cyclohexanecarboxaldehyde (3.2 ml, 26.0 mmol) and *tert*-butylamine (2.8 ml, 26.0 mmol) were reacted as described above (6.4.1) to furnish *tert*-butyl-cyclohexylmethylene-amine (**218**) (4.17g, 95%) as a colourless oil which was used without further purification. Spectral details match those previously reported.<sup>11</sup>

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.08 (9H, s, 3 x  $\text{CH}_3$ ), 1.09-1.29 (5H, m,  $\text{CH}_2$ ), 1.59-1.68 (5H, m,  $\text{CH}_2$ ), 2.04-2.14 (1H, m,  $\text{N}=\text{CHCH}$ ), 7.32 (1H, d,  $J$  6.0,  $\text{N}=\text{CH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 25.76 (2 x t), 26.33 (t), 30.07 (3 x q), 30.34 (2 x t), 44.51 (d), 56.54 (s), 163.48 (d).

## 6.4.1.5 (2-Bromo-benzyl)-cyclohexylmethylene-amine (219)

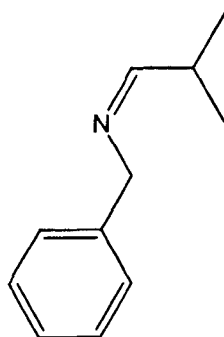




Cyclohexanecarboxaldehyde (1.1 ml, 9.13 mmol) and 2-bromo-benzylamine (1.7 g, 9.12 mmol) were reacted as described above (6.4.1) to yield (2-Bromo-benzyl)-cyclohexylmethylene-amine (**219**) (2.2g, 88%) as a yellow oil which was used without further purification.

$\nu_{\max}$  (film) / $\text{cm}^{-1}$  3027, 2957, 1651, 1522, 1449, 1364, 1172, 1024, 824, 698;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.11-1.32 (5H, m,  $\text{CH}_2$ ), 1.59-1.83 (5H, m,  $\text{CH}_2$ ), 2.15-2.21 (1H, m,  $\text{N}=\text{CHCH}$ ), 4.54 (2H, s,  $\text{NCH}_2$ ), 7.04 (1H, dt,  $J$  7.5,  $J$  1.5, H-5), 7.17-7.28 (2H, m, H-4 and H-6), 7.46 (1H, dd,  $J$  8.0,  $J$  1.0, H-3), 7.60 (1H, d,  $J$  5.0,  $\text{N}=\text{CH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 25.85 (2 x t), 26.40 (t), 30.08 (2 x t), 44.09 (d), 64.67 (t), 123.98 (s), 127.86 (d), 128.73 (d), 130.01 (d), 132.88 (d), 139.15 (s), 171.85 (d);  $m/z$  (EI) 282 [ $(\text{MH}^{81}\text{Br})^+$ , 51%], 280 [ $(\text{MH}^{79}\text{Br})^+$ , 100%], 250 (54), 214 (36), 169 (100), 132 (72).

#### 6.4.1.6 Benzyl-isobutylidene-amine (**220**)<sup>12</sup>

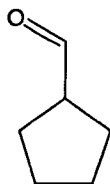


2-Methyl-propionaldehyde (1.7 ml, 18.6 mmol) and benzylamine (2.03 ml, 18.6 mmol) were reacted as described above (6.4.1) to furnish benzyl-isobutylidene-amine (**220**)

(2.82g, 93%) as a colourless oil which was used without further purification. Spectral details match those previously reported.<sup>12</sup>

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.13 (3H, s,  $\text{CH}_3$ ), 1.15 (3H, s,  $\text{CH}_3$ ), 2.48-2.59 (1H, m,  $\text{N}=\text{CHCH}$ ), 4.58 (2H, s,  $\text{NCH}_2$ ), 7.24-7.38 (5H, m, aromatic), 7.69 (1H, app dt,  $J$  5.0,  $J$  1.5,  $\text{N}=\text{CH}$ ), );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 19.76 (2 x q), 34.56 (d), 65.22 (t), 127.23 (d), 128.17 (2 x d), 128.81 (2 x d), 139.85 (s), 171.42 (d).

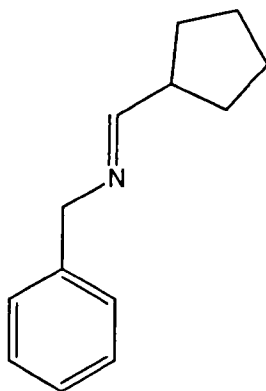
#### 6.4.2 Cyclopentanecarboxaldehyde (221)



Cyclopentanemethanol (2.15 ml, 19.9 mmol) in dichloromethane (20 ml) was added in one portion to a stirred solution of PCC (9.46g, 43.9 mmol) in dichloromethane (60 ml). The resulting mixture was stirred at room temperature for one hour. Diethyl ether (100 ml) was added to the mixture and the whole filtered through a small pad of florisil. Subsequent removal of the solvents under reduced pressure furnished cyclopentanecarboxaldehyde (**221**) (1.2g, 65%) as a pale purple oil.

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.58-1.68 (4H, m,  $\text{CH}_2$ ), 1.79-1.84 (4H, m,  $\text{CH}_2$ ), 2.75 (1H, app dq,  $J$  7.0,  $J$  2.5,  $\text{CHCHO}$ ), 9.62 (1H, d, 2.5,  $\text{CHO}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.22 (2 x t), 26.89 (2 x t), 51.99 (d), 203.72 (d);  $m/z$  (CI) 115 ( $\text{MNH}_4^+$ , 58%), 97 (33), 86 (42), 73 (100), 69 (51), 41 (50).

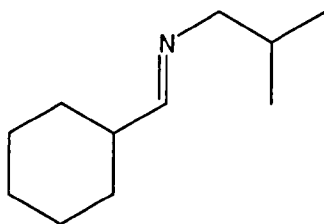
## 6.4.1.7 Benzyl-cyclopentylmethylene-amine (222)



Cyclopentanecarboxaldehyde (1.12 g, 11.0 mmol) and benzylamine (1.24 ml, 11.0 mmol) were reacted as described above (6.4.1) to furnish benzyl-cyclopentylmethylene-amine (**222**) (1.89g, 91%) as a pale brown oil which was used without further purification.

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  3023, 2944, 1652, 1602, 1453, 1347, 1157, 1024, 729;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.56-1.73 (6H, m,  $\text{CH}_2$ ), 1.89-1.95 (2H, m,  $\text{CH}_2$ ), 2.70-2.81 (1H, m,  $\text{N}=\text{CHCH}$ ), 4.56 (2H, s,  $\text{NCH}_2$ ), 7.26-7.39 (5H, m, aromatic), 7.71 (1H, d,  $J$  5.0,  $\text{N}=\text{CH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.12 (2 x t), 30.56 (2 x t), 45.79 (d), 65.18 (t), 127.57 (d), 127.78 (2 x d), 128.82 (2 x d), 139.81 (s), 170.37 (d);  $m/z$  (CI) 204 ( $\text{MNH}_4^+$ , 29%), 136 (71), 108 (66), 91 (100).

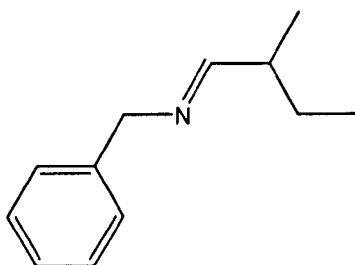
#### 6.4.1.8 Cyclohexylmethylene-isobutyl-amine (223)



Cyclohexanecarboxaldehyde (3.2 ml, 26.0 mmol) and isobutylamine (2.58 ml, 26.0 mmol) were reacted as described above (6.4.1) to yield cyclohexylmethylene-isobutyl-amine (**223**) (4.08g, 93%) as a colourless oil which was used without further purification.

$\nu_{\max}$  (neat) /cm<sup>-1</sup> 3373, 2964, 1652, 1667, 1492, 1374, 829, 696;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 0.79 (6H, d, *J* 6.5, CHCH<sub>3</sub>CH<sub>3</sub>), 1.10-1.29 (5H, m, CH<sub>2</sub>), 1.61-1.74 (5H, m, CH<sub>2</sub>), 1.79 (1H, ddt, *J* 7.0, CH<sub>2</sub>CHCH<sub>3</sub>CH<sub>3</sub>), 2.07-2.11 (1H, m, N=CHCH), 3.09 (2H, d, *J* 6.5, NCH<sub>2</sub>), 7.36 (1H, d, *J* 5.5, N=CH);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 20.84 (2 x q), 25.36 (2 x t), 25.81 (t), 29.46 (d), 30.19 (2 x t), 43.81 (d), 69.91 (t), 169.35 (d); *m/z* (CI) 185 (MNH<sub>4</sub><sup>+</sup>, 63%), 153 (7), 110 (31), 48 (37).

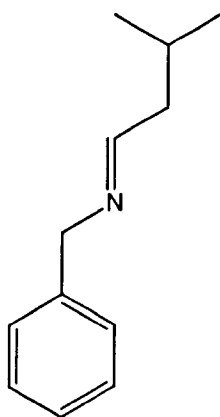
#### 6.4.1.9 Benzyl-(2-methyl-butylidene)-amine (224)<sup>13</sup>



2-Methylbutylaldehyde (3.0 ml, 27.0 mmol) and benzylamine (3.05 ml, 27.0 mmol) were reacted as described above (6.4.1) to yield benzyl-(2-methyl-butylidene)-amine (**224**) (4.63g, 97%) as a colourless oil which was used without further purification. Spectral details match those previously reported.<sup>13</sup>

$\nu_{\max}$  (neat) /cm<sup>-1</sup> 3027, 2962, 2873, 1667, 1494, 1452, 1379, 1027, 696;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 0.95 (3H, t, *J* 7.5, CH<sub>2</sub>CH<sub>3</sub>), 1.11 (3H, d, *J* 7.0, CHCH<sub>3</sub>), 1.38-1.52 (1H, m, CHCH<sub>2</sub>HCH<sub>3</sub>), 1.53-1.67 (1H, m, CHCH<sub>2</sub>HCH<sub>3</sub>), 2.34 (1H, app sp, *J* 7.0, N=CHCH), 4.59 (2H, s, NCH<sub>2</sub>), 7.23-7.39 (5H, m, aromatic H), 7.64 (1H, dt, *J* 6.0, *J* 1.5, N=CH);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 12.03 (q), 17.34 (q), 27.41 (t), 41.44 (d), 65.35 (t), 127.21 (d), 128.19 (2 x d), 128.95 (2 x d), 139.87 (s), 171.09 (d).

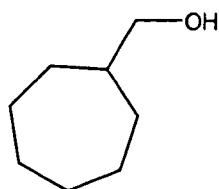
#### 6.4.1.10 Benzyl-(3-methyl-butylidene)-amine (**225**)<sup>14</sup>



3-Methylbutylaldehyde (3.0 ml, 27.0 mmol) and benzylamine (3.05 ml, 27.0 mmol) were reacted as described above (6.4.1) to yield benzyl-(3-methyl-butylidene)-amine (**225**) (4.49g, 94%) as a pale yellow oil which was used without further purification.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  3027, 2866, 1650, 1494, 1453, 1365, 1157, 1027, 731, 697;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 0.99 (6H, d,  $J$  6.5,  $\text{CHCH}_3\text{CH}_3$ ), 1.97 (1H, ddt,  $J$  7.0,  $\text{CH}_2\text{CHCH}_3\text{CH}_3$ ), 2.23 (2H, dd,  $J$  7.0,  $J$  5.5,  $\text{N=CHCH}_2$ ), 4.60 (2H, s,  $\text{NCH}_2$ ), 7.23-7.37 (5H, m, aromatic H), 7.79 (1H, t,  $J$  7.0,  $\text{N=CH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 22.96 (2 x q), 26.74 (d), 45.19 (t), 65.63 (t), 126.82 (d), 128.59 (2 x d), 128.94 (2 x d), 139.76 (s), 166.28 (d).

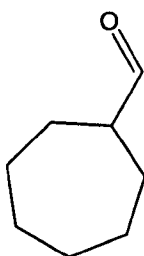
### 6.4.3 Cycloheptyl-methanol (226)<sup>15</sup>



A solution of cycloheptanecarboxylic acid (5.0g, 3.5 mmol) in diethyl ether (25 ml) was added over a period of 30 minutes to a suspension of  $\text{LiAlH}_4$  (4.0g, 10.5 mmol) in diethyl ether (100 ml) under an atmosphere of nitrogen. The mixture was stirred for 90 minutes at room temperature. Excess  $\text{LiAlH}_4$  was destroyed by careful addition of water (15 ml) followed by the addition of 15% sodium hydroxide solution (20 ml). The resulting precipitate was removed by filtration and the filtrate extracted with diethyl ether (3 x 30 ml). The combined extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield cycloheptyl-methanol (**226**) (4.48g, 99%) as a colourless oil. Spectral details match those previously reported.<sup>15</sup>

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.12-1.24 (2H, m,  $\text{CH}_2$ ), 1.37-1.79 (11H, m,  $\text{CH}_2$  and  $\text{CH}$  and  $\text{CH}_2\text{OH}$ ), 3.42 (2H, d,  $J$  7.5,  $\text{CH}_2\text{OH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.89 (2 x t), 28.97 (2 x t), 31.13 (2 x t), 42.46 (d), 69.03 (t).

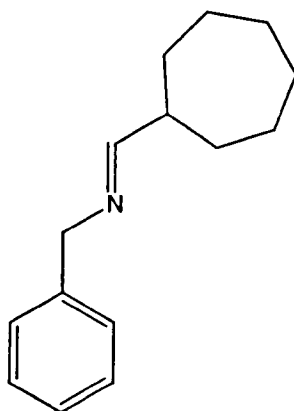
#### 6.4.4 Cycloheptanecarboxaldehyde (**227**)<sup>15</sup>



Cycloheptylmethanol (**58**) (3.0g, 23.0 mmol) in dichloromethane (30 ml) was added in one portion to a stirred solution of PCC (11.11g, 51.5 mmol) in dichloromethane (100 ml). The resulting mixture was stirred at room temperature for one hour. Diethyl ether (150 ml) was added to the mixture and the whole filtered through a small pad of florisil. Subsequent removal of the solvents under reduced pressure furnished cycloheptanecarboxaldehyde (**227**) (2.76g, 95%) as a yellow oil.

$\nu_{\text{max}}$  (film)  $/\text{cm}^{-1}$  2925, 1705, 1461, 1416, 1273, 1225, 942, 876, 833;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.46-1.76 (10H, m,  $\text{CH}_2$ ), 1.90-2.00 (2H, m,  $\text{CH}_2$ ), 2.34-2.42 (1H, m,  $\text{CHCHO}$ ), 9.64 (1H, s,  $\text{CHO}$ ),  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.66 (2 x t), 27.59 (2 x t), 28.94 (2 x t), 52.25 (d), 203.94 (d).

## 6.4.1.11 Benzyl-cycloheptylmethylene-amine (228)



Cycloheptanecarboxaldehyde (**227**) (2.0g, 15.8 mmol) and benzylamine (1.73 ml, 15.8 mmol) were reacted as described above (6.4.1) to yield benzyl-cycloheptylmethylene-amine (**228**) (2.7g, 83%) as a yellow oil which was used without further purification.

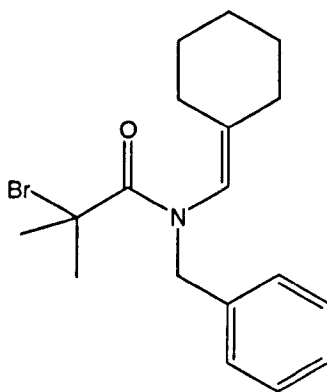
$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  2926, 2862, 1662, 1611, 1517, 1446, 1247, 1177, 1035, 731;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.42-1.75 (10H, m,  $\text{CH}_2$ ), 1.81-1.96 (2H, m,  $\text{CH}_2$ ), 2.36-2.41 (1H, m,  $\text{N}=\text{CHCH}$ ), 4.56 (2H, s,  $\text{NCH}_2$ ), 7.20-7.37 (5H, m, aromatic H), 7.69 (1H, d,  $J$  5.0,  $\text{N}=\text{CH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.97 (2 x t), 28.75 (2 x t), 30.83 (2 x t), 45.62 (d), 65.21 (t), 127.75 (d), 128.19 (2 x d), 128.37 (2 x d), 139.88 (s), 171.15 (d);  $m/z$  (EI) 216 ( $\text{MH}^+$ , 12%), 158 (82), 91 (100).



### 6.4.5 General procedure for the preparation of bromo-enamides

To a stirred solution of methylene-amine in dry dichloromethane under an atmosphere of nitrogen was added 2-bromo-2-methylpropionyl bromide (1.1 eq.) dropwise. Diethylaniline (1.1 eq.) was then added dropwise and the mixture stirred for two hours at room temperature. The resulting mixture was washed with a 10% solution of HCl (2 x 20 ml) followed by a saturated solution sodium chloride (2 x 50 ml). The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield the crude product.

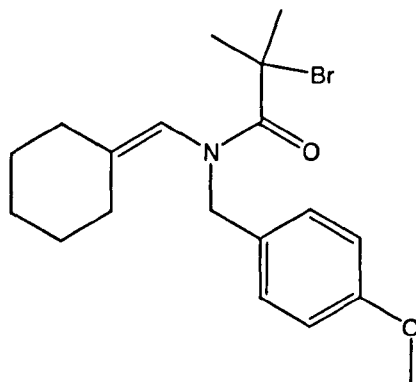
#### 6.4.5.1 *N*-Benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methypropionamide (119)



To a solution of benzyl-cyclohexylmethylene-amine (**215**) (1.0g, 4.97 mmol) was added 2-bromo-2-methylpropionyl bromide (0.61 ml, 5.46 mmol). Purification by flash column chromatography eluting with 5:2 petroleum ether:ethyl acetate afforded *N*-benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methypropionamide (**119**) (0.93g, 58%) as a pale yellow oil.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  3028, 2929, 1737, 1639, 1495, 1390, 1365, 1178, 749, 698;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.48-1.56 (6H, m,  $\text{CH}_2$ ), 2.06 (6H, s, 2 x  $\text{CH}_3$ ), 2.11-2.15 (4H, m,  $\text{CH}_2$ ), 4.69 (2H, s,  $\text{NCH}_2\text{Ph}$ ), 6.32 (1H, s,  $\text{NCH}$ ), 7.23-7.34 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.45 (t), 26.62 (t), 27.84 (t), 28.96 (t), 32.71 (2 x q), 33.21 (t), 55.45 (t), 58.9 (s), 123.16 (d), 127.53 (d), 128.26 (2 x d), 128.79 (2 x d), 137.74 (s), 141.54 (s), 171.04 (s);  $m/z$  (EI) 352 [ $(\text{MH}^{81}\text{Br})^+$ , 34%], 350 [ $(\text{MH}^{79}\text{Br})^+$ , 34%], 270 (86), 200 (27), 178 (52), 111 (73), 91 (100); (Found:  $\text{MH}^+$ , 350.1082.  $\text{C}_{18}\text{H}_{24}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 350.1079).

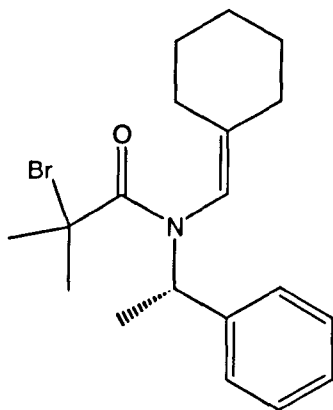
#### 6.4.5.2 2-Bromo-*N*-cyclohexylidenemethyl-*N*-(4-methoxy-benzyl)-2-methyl-propionamide (126)



To a solution of cyclohexylmethylene-(4-methoxy-benzyl)-amine (**216**) (2.0g, 9.3 mmol) was added 2-bromo-2-methylpropionyl bromide (1.14 ml, 10.2 mmol). Purification by flash column chromatography eluting with 6:1 petroleum ether:ethyl acetate furnished bromo-*N*-cyclohexylidenemethyl-*N*-(4-methoxy-benzyl)-2-methyl-propionamide (**126**) (1.43g, 55%) as a pale yellow oil.

$\nu_{\max}$  (film) / $\text{cm}^{-1}$  2930, 2853, 2834, 1737, 1639, 1612, 1512, 1390, 1247, 1174, 835, 737;  
 $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.48-1.62 (6H, m,  $\text{CH}_2$ ), 1.99 (6H, s, 2 x  $\text{CH}_3$ ), 2.06-2.13 (4H, m,  $\text{CH}_2$ ), 3.81 (3H, s,  $\text{OCH}_3$ ), 4.62 (2H, s,  $\text{NCH}_2\text{Ar}$ ), 6.27 (1H, s,  $\text{NCH}$ ), 6.86 (2H, d,  $J$  9.0, aromatic H), 7.19 (2H, d,  $J$  9.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.45 (t), 26.63 (t), 27.86 (t) 28.95 (t), 32.71 (2 x q), 33.22 (t), 54.82 (t), 55.62 (q), 58.99 (s), 114.14 (2 x d), 123.09 (d), 129.75 (2 x d), 129.92 (s), 141.49 (s), 159.15 (s), 170.91 (s);  $m/z$  (EI) 381  $[(\text{M}-^{81}\text{Br})^+, 34\%]$ , 379  $[(\text{M}-^{79}\text{Br})^+, 34\%]$ , 300 (100), 230 (12), 182 (33), 121 (83).

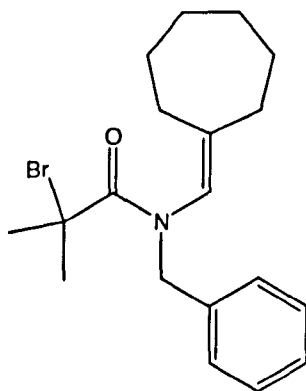
#### 6.4.5.3 2-Bromo-*N*-cyclohexylidenemethyl-2-methyl-*N*-(1-phenyl-ethyl)-propionamide (130)



To a solution of cyclohexylmethylene-(1-phenyl-ethyl)-amine (**217**) (2.9g, 13.0 mmol) was added 2-bromo-2-methylpropionyl bromide (1.66 ml, 14.3 mmol). Purification by flash column chromatography eluting with 9:1 petroleum ether:ethyl acetate afforded 2-bromo-*N*-cyclohexylidenemethyl-2-methyl-*N*-(1-phenyl-ethyl)-propionamide (**130**) (2.50g, 58%) as a colourless oil.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  2927, 1739, 1691, 1637, 1486, 1364, 1177, 750;  $\delta_{\text{H}}$ (250 MHz,  $\text{CDCl}_3$ ) 1.11-1.69 (6H, m,  $\text{CH}_2$ ), 1.47 (3H, d,  $J$  7.0,  $\text{NCH}(\text{CH}_3)\text{Ph}$ ), 1.92 (6H, s, 2 x  $\text{CH}_3$ ), 1.98-2.10 (4H, m,  $\text{CH}_2$ ), 5.75 (1H, s,  $\text{NCH}=\text{C}$ ), 5.91 (1H, q,  $J$  7.0,  $\text{NCH}(\text{CH}_3)\text{Ph}$ ), 7.19-7.32 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 16.92 (q), 26.35 (t), 26.51 (t), 27.63 (t), 29.34 (t), 33.24 (q), 33.35 (q), 33.61 (t), 56.40 (d), 60.06 (s), 118.81 (d), 127.71 (2 x d), 128.47 (d), 128.71 (2 x d), 140.83 (s), 144.83 (s), 171.32 (s);  $m/z$  (EI) 366  $[(\text{MH}^{81}\text{Br})^+, 87\%]$ , 364  $[(\text{MH}^{79}\text{Br})^+, 100\%]$ , 300 (54), 284 (100), 180 (85), 105 (96); (Found:  $\text{MH}^+$ , 364.1280.  $\text{C}_{19}\text{H}_{26}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 364.1277).

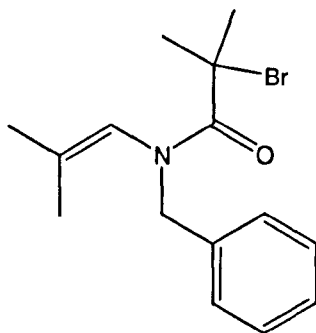
#### 6.4.5.4 *N*-Benzyl-2-bromo-*N*-cycloheptylidene-methyl-2-methyl-propionamide (123)



To a solution of benzyl-cycloheptylmethylene-amine (**228**) (2.57g, 12.0 mmol) was added 2-bromo-2-methylpropionyl bromide (1.4 ml, 13.0 mmol). Purification by flash column chromatography eluting with 9:1 petroleum ether:ethyl acetate afforded *N*-benzyl-2-bromo-*N*-cycloheptylidene-methyl-2-methyl-propionamide (**123**) (2.75g, 63%) as a colourless oil.

$\nu_{\max}$  (nujol) /cm<sup>-1</sup> 3027, 2929, 1725, 1640, 1448, 1367, 1176, 987, 837;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.54-1.62 (8H, m, 4 x CH<sub>2</sub>), 1.98 (6H, s, 2 x CH<sub>3</sub>), 2.28-2.33 (4H, m, 2 x CH<sub>2</sub>), 4.69 (2H, s, NCH<sub>2</sub>Ph), 6.39 (1H, s, NCH), 7.23-7.33 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 26.07 (t), 28.75 (t), 29.85 (t), 30.74 (2 x t), 32.48 (2 x q), 34.24 (t), 54.56 (t), 58.88 (s), 126.04 (d), 127.49 (d), 128.09 (2 x d), 128.79 (2 x d), 137.85 (s), 143.91 (s), 170.83 (s);  $m/z$  (EI) 366 [(MH-<sup>81</sup>Br)<sup>+</sup>, 100%], 364 [(MH-<sup>79</sup>Br)<sup>+</sup>, 100%], 300 (29), 284 (86), 178 (65), 108 (76), 91 (30); (Found: MH<sup>+</sup>, 364.1263. C<sub>19</sub>H<sub>26</sub><sup>79</sup>BrNO requires MH<sup>+</sup>, 364.1277).

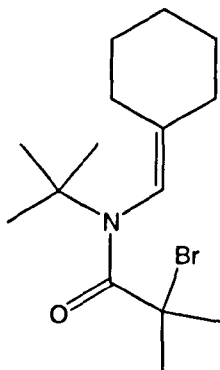
#### 6.4.5.5 *N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-propenyl)-propionamide (121)



To a solution of benzyl-isobutylidene-amine (**220**) (2.0g, 12.0 mmol) was added 2-bromo-2-methylpropionyl bromide (1.53 ml, 13.1 mmol). Purification by flash column chromatography eluting with 6:1 petroleum ether:ethyl acetate furnished *N*-benzyl-2-bromo-2-methyl-*N*-(2-methyl-propenyl)-propionamide (**121**) (2.75g, 74%) as a colourless oil.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  3028, 2974, 1737, 1640, 1495, 1463, 1353, 1179, 1108, 831, 699, 620;  
 $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.62 (3H, s,  $\text{C}=\text{CCH}_3\text{CH}_3$ ), 1.73 (3H, s,  $\text{C}=\text{CCH}_3\text{CH}_3$ ), 1.98 (6H, s, 2 x  $\text{CH}_3$ ), 4.70 (2H, s,  $\text{CH}_2$ ), 6.35 (1H, s,  $\text{NCH}$ ), 7.24-7.35 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 18.56 (q), 21.48 (q), 32.46 (2 x q), 54.82 (t), 58.69 (s), 126.13 (d), 127.53 (d), 128.22 (2 x d), 128.81 (2 x d), 135.33 (s), 137.67 (s), 171.01 (s);  $m/z$  (EI) 312 [(MH- $^{81}\text{Br}$ ) $^+$ , 76%], 310 [(MH- $^{79}\text{Br}$ ) $^+$ , 77%], 247 (65), 230 (100), 140 (27), 91 (51); (Found:  $\text{MH}^+$ , 310.0785.  $\text{C}_{15}\text{H}_{20}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 310.0779).

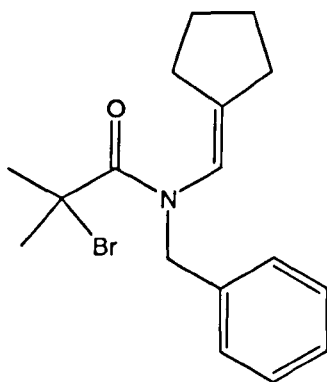
#### 6.4.5.6 2-Bromo-*N-tert*-butyl-*N*-cyclohexylidenemethyl-2-methyl-propionamide (127)



To a solution of *tert*-butyl-cyclohexylmethylene-amine (**218**) (3.71g, 22.0 mmol) was added 2-bromo-2-methylpropionyl bromide (2.74 ml, 24.2 mmol). Purification by flash column chromatography eluting with 9:1 petroleum ether:ethyl acetate afforded 2-bromo-*N-tert*-butyl-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**127**) (1.95g, 28%) as a pale yellow oil.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  2929, 2855, 1738, 1640, 1448, 1366, 1179, 1078, 837;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.39 (9H, s, *tert*-Bu 3 x  $\text{CH}_3$ ), 1.43-2.12 (8H, m,  $\text{CH}_2$ ), 1.86 (3H, s,  $\text{C}(\text{Br})\text{CH}_3\text{CH}_3$ ), 1.96 (3H, s,  $\text{C}(\text{Br})\text{CH}_3\text{CH}_3$ ), 2.24-2.36 (2H, m,  $\text{CH}_2$ ), 6.05 (1H, s, *NCH*);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.59 (t), 26.75 (t), 27.66 (t), 28.66 (3 x q), 29.31 (t), 32.94 (q), 33.44 (t), 34.68 (q), 60.52 (s), 62.31 (s), 121.56 (d), 143.09 (s), 171.77 (s);  $m/z$  (EI) 318  $[(\text{MH}^{81}\text{Br})^+]$ , 58%, 316  $[(\text{MH}^{79}\text{Br})^+]$ , 59%, 236 (42), 194 (20).

#### 6.4.5.7 *N*-Benzyl-2-bromo-*N*-cyclopentylidenemethyl-2-methyl-propionamide (**122**)

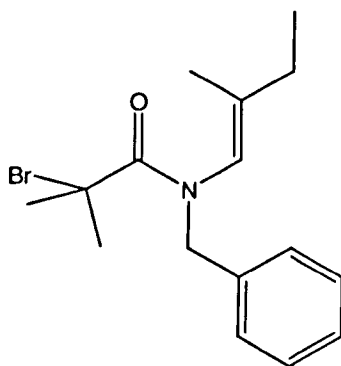


To a solution of benzyl-cyclopentylmethylene-amine (**212**) (1.75g, 9.0 mmol) was added 2-bromo-2-methylpropionyl bromide (1.15 ml, 9.0 mmol). Purification by flash column chromatography eluting with 5:1 petroleum ether:ethyl acetate afforded *N*-benzyl-2-bromo-*N*-cyclopentylidenemethyl-2-methyl-propionamide (**122**) (1.61g, 53%) as a pale yellow oil.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  3033, 2927, 1717, 1497, 1374, 1178, 751, 663;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.65-1.73 (4H, m,  $\text{CH}_2$ ), 1.99 (6H, s, 2 x  $\text{CH}_3$ ), 2.19-2.23 (2H, m,  $\text{CH}_2$ ), 2.30-2.34 (2H,

m,  $\text{CH}_2$ ), 4.75 (2H, s,  $\text{NCH}_2$ ), 6.57 (1H, s,  $\text{NCH}$ ), 7.24-7.35 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.25 (t), 26.30 (t), 30.12 (t), 31.57 (t), 32.42 (2 x q), 53.59 (t), 58.77 (s), 122.65 (d), 127.44 (d), 127.91 (2 x d), 128.79 (2 x d), 138.04 (s), 145.27 (s), 170.58 (s);  $m/z$  (EI) 338  $[(\text{MH}-^{81}\text{Br})^+, 96\%]$ , 336  $[(\text{MH}-^{79}\text{Br})^+, 100\%]$ , 256 (80), 186 (9), 166 (21), 91 (17); (Found:  $\text{MH}^+$ , 336.0976.  $\text{C}_{17}\text{H}_{22}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 336.0979).

#### 6.4.5.8 *N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-but-1-enyl)-propionamide (**124**)



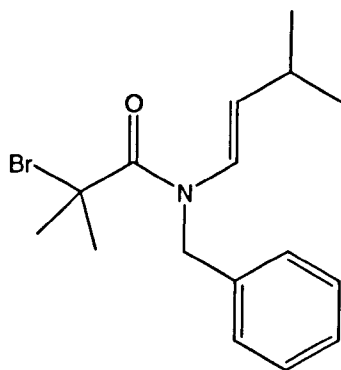
To a solution of benzyl-(2-methyl-butylidene)-amine (**224**) (3.0g, 17.0 mmol) was added 2-bromo-2-methylpropionyl bromide (2.1 ml, 18.7 mmol). Purification by flash column chromatography eluting with 9:1 petroleum ether:ethyl acetate furnished *N*-benzyl-2-bromo-2-methyl-*N*-(2-methyl-but-1-enyl)-propionamide (**124**) (2.52g, 52%) as a colourless oil.

$\nu_{\text{max}}$  (film) / $\text{cm}^{-1}$  3029, 2966, 1737, 1638, 1495, 1462, 1365, 1262, 1178, 1108, 845, 698;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.04 (3H, t,  $J$  7.5,  $\text{CH}_2\text{CH}_3$ ), 1.61 (3H, s,  $\text{C}=\text{CCH}_3$ ), 1.98 (6H, s, 2 x  $\text{CH}_3$ ), 2.10 (2H, q,  $J$  7.5,  $\text{CH}_2\text{CH}_3$ ), 4.69 (2H, s,  $\text{NCH}_2$ ), 6.36 (1H, s,  $\text{NCH}$ ), 7.23-7.33 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 11.21 (q), 14.60 (q), 29.36 (t), 32.45 (2 x q),



54.72 (t), 58.87 (s), 125.56 (d), 127.54 (d), 128.38 (2 x d), 128.78 (2 x d), 137.68 (s), 140.17 (s), 170.97 (s);  $m/z$  (CI) 326 [(MH- $^{81}\text{Br}$ ) $^+$ , 76%], 324 [(MH- $^{79}\text{Br}$ ) $^+$ , 80%], 294 (22), 244 (85), 91 (38); (Found: MH $^+$ , 324.0966 C<sub>16</sub>H<sub>22</sub> $^{79}\text{BrNO}$  requires MH $^+$ , 324.0964).

#### 6.4.5.9 *N*-Benzyl-2-bromo-2-methyl-*N*-(3-methyl-but-1-enyl)-propionamide (125)

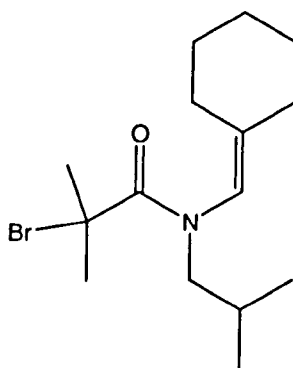


To a solution of benzyl-(3-methyl-butyldiene)-amine (**225**) (3.0g, 17.0 mmol) was added 2-bromo-2-methylpropionyl bromide (2.1 ml, 18.7 mmol). Purification by flash column chromatography eluting with 6:1 petroleum ether:ethyl acetate afforded *N*-benzyl-2-bromo-2-methyl-*N*-(3-methyl-but-1-enyl)-propionamide (**125**) (2.9g, 60%) as a pale yellow oil.

$\nu_{\text{max}}$  (neat) /cm $^{-1}$  2974, 1737, 1641, 1496, 1390, 1262, 1179, 1079, 830, 699;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.00 (6H, d,  $J$  7.0, CHCH<sub>3</sub>CH<sub>3</sub>), 2.02 (6H, s, CBrCH<sub>3</sub>CH<sub>3</sub>), 2.35 (1H, m, CHCHCH<sub>3</sub>CH<sub>3</sub>), 4.94 (2H, s, NCH<sub>2</sub>), 5.10 (1H, dd,  $J$  7.5,  $J$  6.5, NC=CH), 7.16-7.39 (5H, m, aromatic H), 7.32 (1H, d,  $J$  6.5, NCH);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 23.08 (2 x q), 29.79 (d), 32.99 (2 x q), 50.41 (t), 57.51 (s), 122.74 (2 x d), 126.84 (2 x d), 127.24 (d), 128.91 (2 x

d), 137.67 (s), 169.40 (s);  $m/z$  (CI) 326 [(MH- $^{81}\text{Br}$ ) $^+$ , 65%], 324 [(MH- $^{79}\text{Br}$ ) $^+$ , 66%], 244 (24), 176 (52), 91 (77).

**6.4.5.10 2-Bromo-*N*-cyclohexylidenemethyl-*N*-isobutyl-2-methyl-propionamide (128)**

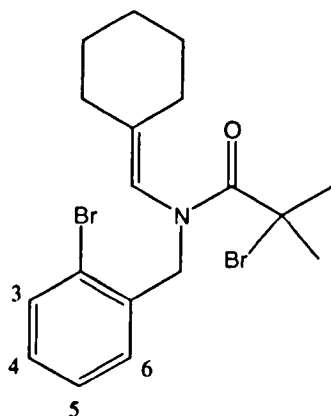


To a solution of cyclohexylmethylene-isobutyl-amine (**223**) (4.38g, 26.0 mmol) was added 2-bromo-2-methylpropionyl bromide (3.2 ml, 28.6 mmol). Purification by flash column chromatography eluting with 5:1 petroleum ether:ethyl acetate afforded 2-bromo-*N*-cyclohexylidenemethyl-*N*-isobutyl-2-methyl-propionamide (**128**) (3.8g, 47%) as a colourless oil.

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  2929, 1736, 1645, 1463, 1389, 1173, 833;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 0.88 (6H, d,  $J$  7.0,  $\text{CHCH}_3\text{CH}_3$ ), 1.56-1.65 (6H, m,  $\text{CH}_2$ ), 1.95 (6H, s,  $\text{CBrCH}_3\text{CH}_3$ ), 2.04-2.11 (3H, m,  $\text{CH}_2$  and  $\text{CH}_2\text{CHCH}_3\text{CH}_3$ ), 2.13-2.17 (2H, m,  $\text{CH}_2$ ), 3.31 (2H, d,  $J$  7.5,  $\text{NCH}_2$ ), 6.49 (1H, s,  $\text{NCH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 20.72 (2 x q), 26.45 (t), 26.56 (t), 27.12 (d), 27.84 (t), 27.92 (t), 32.77 (2 x q), 33.23 (t), 59.36 (s), 59.79 (t), 123.82 (d),

140.23 (s), 170.72 (s);  $m/z$  (EI) 318  $[(MH-^{81}Br)^+, 43\%]$ , 316  $[(MH-^{79}Br)^+, 45\%]$ , 236 (18), 180 (38); (Found:  $MH^+$ , 316.1278  $C_{15}H_{26}^{79}BrNO$  requires  $MH^+$ , 316.1277).

**6.4.5.11 2-Bromo-*N*-(2-bromo-benzyl)-*N*-cyclohexylidenemethyl-2-methyl-propionamide (129)**

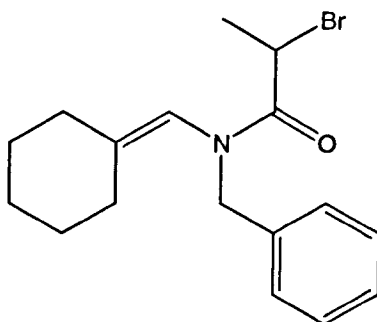


To a solution of (2-bromo-benzyl)-cyclohexylmethylene-amine (**219**) (2.0g, 7.14 mmol) was added 2-bromo-2-methylpropionyl bromide (0.88 ml, 8.14 mmol). Purification by flash column chromatography eluting with 9:1 petroleum ether:ethyl acetate furnished 2-bromo-*N*-(2-bromo-benzyl)-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**129**) (2.02g, 66%) as a colourless oil.

$\nu_{max}$  (film)  $/cm^{-1}$  2930, 2853, 1726, 1641, 1568, 1463, 1444, 1390, 1288, 1108, 1030, 834, 746;  $\delta_H$ (300 MHz,  $CDCl_3$ ) 1.54-1.62 (6H, m,  $CH_2$ ), 2.02 (6H, s,  $CBrCH_3CH_3$ ), 2.06-2.11 (2H, m,  $CH_2$ ), 2.18-2.23 (2H, m,  $CH_2$ ), 4.79 (2H, s,  $NCH_2$ ), 6.39 (1H, s,  $NCH$ ), 7.12 (1H, dt,  $J$  7.5,  $J$  1.5, H-5), 7.26-7.32 (2H, m, H-4 and H-6), 7.52 (1H, d,  $J$  8.0, H-3),  $\delta_C$ (75.5 MHz,  $CDCl_3$ ) 26.33 (t), 26.57 (t), 27.63 (t), 28.98 (t), 32.64 (2 x q),

33.17 (t), 55.41 (t), 58.88 (s), 122.98 (d), 123.64 (s), 127.98 (d), 128.91 (2 x d), 133.71 (d), 136.71 (s), 141.99 (s), 171.12 (s);  $m/z$  (EI) 432 [(MH- $^{81}\text{Br}$   $^{81}\text{Br}$ ) $^+$ , 76%], 430 [(MH- $^{81}\text{Br}$   $^{79}\text{Br}$ ) $^+$ , 100%], 428 [(MH- $^{79}\text{Br}$   $^{79}\text{Br}$ ) $^+$ , 75%], 350 (96), 270 (37), 169 (68).

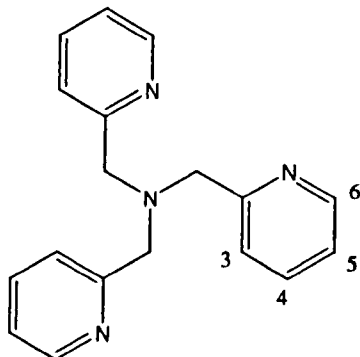
#### 6.4.5.12 *N*-Benzyl-2-bromo-*N*-cyclohexylidenemethyl-propionamide (**120**)



To a solution of benzyl-cyclohexylmethylene-amine (**215**) (2.0g, 9.95 mmol) was added 2-bromopropionyl bromide (1.04 ml, 10.9 mmol). Purification by flash column chromatography eluting with 9:1 petroleum ether:ethyl acetate afforded *N*-benzyl-2-bromo-*N*-cyclohexylidenemethyl-propionamide (**120**) (1.35g, 40%) as a pale yellow oil.

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  2927, 2836, 1719, 1644, 1612, 1468, 1244, 1114, 743;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.43-1.54 (6H, m,  $\text{CH}_2$ ), 1.77 (3H, d,  $J$  6.5,  $\text{CHCH}_3$ ), 1.82-1.88 (2H, m,  $\text{CH}_2$ ), 1.99-2.06 (2H, m,  $\text{CH}_2$ ), 4.58 (1H, d,  $J$  6.5,  $\text{NCHH}$ ), 4.64 (1H, d,  $J$  6.5,  $\text{NCHH}$ ), 4.65 (1H, q,  $J$  6.5,  $\text{CHCH}_3$ ), 5.76 (1H, s,  $\text{NCH}$ ), 7.21-7.26 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 21.40 (q), 24.10 (t), 24.53 (t), 26.84 (t), 27.12 (t), 31.53 (t), 38.48 (d), 53.17 (t), 119.54 (d), 127.98 (d), 128.31 (2 x d), 128.75 (2 x d), 137.89 (s), 146.73 (s), 170.15 (s);  $m/z$  (EI) 338 [(MH- $^{81}\text{Br}$ ) $^+$ , 85%], 336 [(MH- $^{79}\text{Br}$ ) $^+$ , 100%], 256 (100), 200 (7), 91 (100).

#### 6.4.6 Tris-(2-pyridyl-methyl)-amine (132)



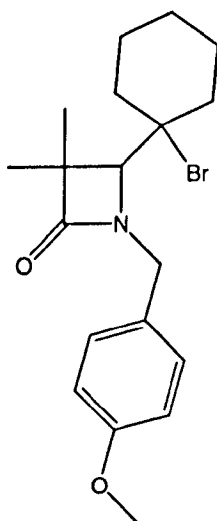
To a solution of 2-picolyl chloride hydrochloride (9.75g, 59.5 mmol) in deionized water (25 ml) at 0°C was added with stirring a 5.3 N aqueous solution of sodium hydroxide (12 ml). The resulting free amine appeared as a red emulsion following the neutralisation. To this mixture was added a solution of 2-(aminomethyl)pyridine (3.2g, 29.5 mmol) in dichloromethane (50 ml). The resulting mixture was allowed to warm to room temperature and, over a 48 hour period, an additional aliquot of 5.3 N aqueous sodium hydroxide solution (12 ml) was added. During this addition the pH of the aqueous portion of the reaction mixture was not permitted to exceed 9.5. The mixture was then washed with a 15% sodium hydroxide solution (2 x 50 ml) and the organic phase dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure yielded a solid mass which was extracted with boiling diethyl ether (3 x 30 ml). Removal of the solvent followed by recrystallisation from diethyl ether afforded tris-(2-pyridyl-methyl)-amine (132) (6.4g, 80%) as a white crystalline solid; m.p. 82-83°C.

$\nu_{\max}$  (film) / $\text{cm}^{-1}$  2818, 1589, 1569, 1475, 1437, 1368, 1124, 766;  $\delta_{\text{H}}$ (250 MHz,  $\text{CDCl}_3$ ) 3.72 (6H, s, 3 x  $\text{NCH}_2$ ), 6.98 (3H, t,  $J$  6.0, 3 x H-5), 7.41 (3H, d,  $J$  7.5, 3 x H-3), 7.49 (3H, t,  $J$  7.5, 3 x H-4), 8.36 (3H, d,  $J$  5.0, 3 x H-6);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 59.92 (3 x t), 121.76 (3 x d), 122.69 (3 x d), 136.39 (3 x d), 148.86 (3 x d), 159.12 (3 x s);  $m/z$  (EI) 291 ( $\text{MH}^+$ , 80%), 171 (13), 198 (100), 93 (100).

#### 6.4.7 General procedure for the cyclisation of bromo-enamides.

To a mixture of bromo-enamide and copper (I) bromide (30 mol%) under a nitrogen atmosphere was added a solution of tris-(2-pyridyl-methyl)-amine (**132**) (30 mol%) in dry dichloromethane (0.12M solution). The resulting mixture was stirred at room temperature and upon completion was eluted through a silica plug with dichloromethane. Subsequent removal of solvent under reduced pressure furnished the  $\beta$ -lactam as a colourless oil.

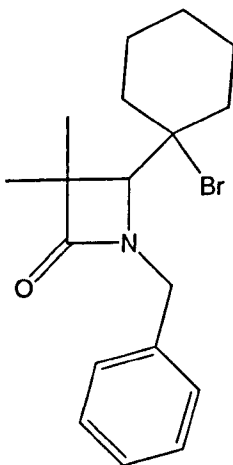
##### 6.4.7.1 4-(1-Bromo-cyclohexyl)-1-(4-methoxy-benzyl)-3,3-dimethyl-azetidin-2-one (**134**)



2-Bromo-*N*-cyclohexylidenemethyl-*N*-(4-methoxy-benzyl)-2-methyl-propionamide (**126**) (100 mg, 0.26 mmol) was reacted as described above (6.4.7) to furnish 4-(1-bromo-cyclohexyl)-1-(4-methoxy-benzyl)-3,3-dimethyl-azetidin-2-one (**134**) (98 mg, 98%) as a colourless oil.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2934, 1751, 1614, 1514, 1246, 1176, 1034, 831;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.24 (3H, s, *CH*<sub>3</sub>), 1.44 (3H, s, *CH*<sub>3</sub>), 1.41-2.15 (10H, m, *CH*<sub>2</sub>), 3.44 (1H, s, *NCH*), 3.76 (3H, s, *OCH*<sub>3</sub>), 4.04 (1H, d, *J* 18.0, *NCHH*), 4.85 (1H, d, *J* 18.0, *NCHH*), 6.83 (2H, d, *J* 8.0, aromatic H), 7.16 (2H, d, *J* 8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 18.73 (q), 22.32 (t), 22.97 (t), 24.85 (q), 25.39 (t), 37.65 (t), 37.96 (t), 45.22 (t), 55.62 (q), 55.77 (s), 72.77 (d), 74.94 (s), 114.41 (2 x d), 128.5 (s), 130.03 (2 x d), 159.39 (s), 175.33 (s); *m/z* (EI) 382 [(MH-<sup>81</sup>Br)<sup>+</sup>, 89%], 380 [(MH-<sup>79</sup>Br)<sup>+</sup>, 100%], 316 (62), 299 (45), 136 (36), 121 (100); (Found: MH<sup>+</sup>, 380.1183. C<sub>19</sub>H<sub>26</sub><sup>79</sup>BrNO<sub>2</sub> requires MH<sup>+</sup>, 380.1179).

#### 6.4.7.2 1-Benzyl-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (**133**)

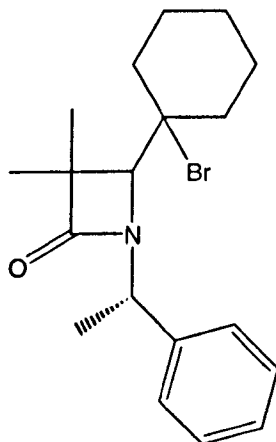


*N*-Benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methypropionamide (**119**) (100 mg, 0.28 mmol) was reacted as described above (6.4.7) to furnish 1-benzyl-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (**133**) (96 mg, 96%) as a colourless oil.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2962, 1646, 1521, 1466, 1438, 1265, 740, 705;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.24 (3H, s, *CH*<sub>3</sub>), 1.42 (3H, s, *CH*<sub>3</sub>), 1.31-2.07 (10H, m, *CH*<sub>2</sub>), 3.35 (1H, s, *NCH*), 4.04 (1H, d, *J* 18.0, *NCHH*), 4.85 (1H, d, *J* 18.0, *NCHH*), 7.18-7.3 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 18.76 (q), 22.31 (t), 22.97 (t), 24.9 (q), 25.38 (t), 37.67 (t), 37.92 (t), 45.83 (t), 55.87 (s), 72.03 (d), 74.76 (s), 128.04 (d), 128.75 (2 x d), 129.1 (2 x d), 136.49 (s), 175.36 (s); *m/z* (EI) 353 [(MH-<sup>81</sup>Br)<sup>+</sup>, 78%], 351 [(MH-<sup>79</sup>Br)<sup>+</sup>, 80%], 270 (46), 137 (100), 91 (83); (Found: MH<sup>+</sup>, 350.1116. C<sub>18</sub>H<sub>24</sub><sup>79</sup>BrNO requires MH<sup>+</sup>, 350.1119).

#### 6.4.7.3 4-(1-Bromo-cyclohexyl)-3,3-dimethyl-1-(1-phenyl-ethyl)-azetidin-2-one

(**146**)

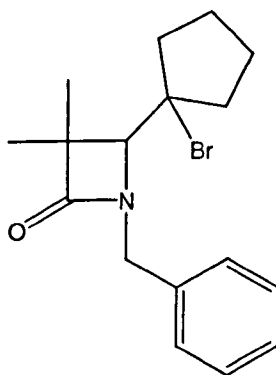




2-Bromo-*N*-cyclohexylidenemethyl-2-methyl-*N*-(1-phenyl-ethyl)-propionamide (130) (100 mg, 0.27 mmol) was reacted as described above (6.4.7) to afford 4-(1-bromo-cyclohexyl)-3,3-dimethyl-1-(1-phenyl-ethyl)-azetidin-2-one (146) (97 mg, 97%) as a colourless oily mixture of two isomers (ratio 1:1).

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2929, 1714, 1628, 1463, 1387, 1288, 1029, 932, 836;  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>) 0.75-2.06 (10H, m, CH<sub>2</sub>) 1.15 (3/2H, s, CH<sub>3</sub>), 1.29 (3/2H, s, CH<sub>3</sub>), 1.36 (3/2H, s, CH<sub>3</sub>), 1.38 (3/2H, s, CH<sub>3</sub>), 1.66 (3/2H, d, *J* 7.5, NCH(CH<sub>3</sub>)Ph), 1.81 (3/2, d, *J* 7.5, NCH(CH<sub>3</sub>)Ph), 3.41 (1/2H, s, NCH), 3.62 (1/2H, s, NCH), 4.67 (1/2H, q, *J* 7.5, NCH(CH<sub>3</sub>)Ph), 4.78 (1/2H, q, *J* 7.5, NCH(CH<sub>3</sub>)Ph), 7.19-7.29 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) *mixture* 17.49 (q), 17.61 (q), 19.35 (q), 19.82 (q), 20.87 (2 x t), 21.65 (2 x t), 23.23 (q), 23.84 (q), 23.90 (t), 36.27 (s), 36.78 (s), 53.39 (s), 53.66 (s), 54.06 (d), 54.82 (d), 71.31 (d), 74.19 (d), 125.91 (2 x d), 126.29 (2 x d), 126.34 (d), 126.51 (d), 127.49 (2 x d), 127.69 (2 x d), 140.42 (s), 141.08 (s), 174.13 (s), 174.25 (s); *m/z* (EI) 366 [(MH-<sup>81</sup>Br)<sup>+</sup>, 100%], 364 [(MH-<sup>79</sup>Br)<sup>+</sup>, 98%], 284 (100), 136 (100), 105 (36), 83 (100).

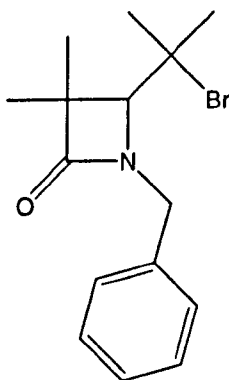
6.4.7.4 1-Benzyl-4-(1-bromo-cyclopentyl)-3,3-dimethyl-azetidin-2-one (143)



*N*-Benzyl-2-bromo-*N*-cyclopentylidenemethyl-2-methyl-propionamide (**122**) (100 mg, 0.30 mmol) was reacted as described above (6.4.7) to furnish 1-benzyl-4-(1-bromocyclopentyl)-3,3-dimethyl-azetidin-2-one (**143**) (94 mg, 94%) as a colourless oil.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2934, 1697, 1574, 1455, 1263, 1137, 926, 701;  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>) 1.26 (3H, s, *CH*<sub>3</sub>), 1.38 (3H, s, *CH*<sub>3</sub>), 1.50-1.92 (6H, m, *CH*<sub>2</sub>), 2.10-2.25 (2H, m, *CH*<sub>2</sub>), 3.35 (1H, s, *NCH*), 3.95 (1H, d, *J* 15.5, *NCHH*), 4.86 (1H, d, *J* 15.5 Hz, *NCHH*), 7.15-7.28 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 16.42 (q), 21.84 (t), 22.86 (t), 23.04 (q), 28.69 (t), 40.45 (t), 44.09 (t), 54.32 (s), 69.16 (d), 74.69 (s), 126.71 (d), 127.12 (2 x d), 127.80 (2 x d), 134.89 (s), 173.70 (s); *m/z* (EI) 368 [(MH-<sup>81</sup>Br)<sup>+</sup>, 100%], 366 [(MH-<sup>79</sup>Br)<sup>+</sup>, 83%], 256 (92), 186 (30), 122 (100), 91 (56).

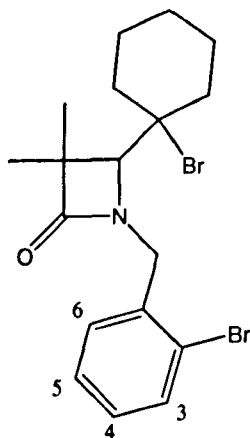
#### 6.4.7.5 1-Benzyl-4-(1-bromo-1-methyl-ethyl)-3,3-dimethyl-azetidin-2-one (**141**)



*N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-propenyl)-propionamide (**121**) (200 mg, 0.62 mmol) was reacted as described above (6.4.7) to furnish 1-benzyl-4-(1-bromo-1-methylethyl)-3,3-dimethyl-azetidin-2-one (**141**) (194 mg, 97%) as a colourless oil.

$\nu_{\max}$  (film) / $\text{cm}^{-1}$  2928, 1695, 1600, 1582, 1457, 1377, 1288, 933, 710;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.20 (3H, s,  $\text{CH}_3$ ), 1.32 (3H, s,  $\text{CH}_3$ ), 1.73 (3H, s,  $\text{C}(\text{Br})\text{CH}_3\text{CH}_3$ ), 1.74 (3H, s,  $\text{C}(\text{Br})\text{CH}_3\text{CH}_3$ ), 3.53 (1H, s,  $\text{NCH}$ ), 4.15 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 4.85 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 7.18-7.27 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 18.28 (q), 19.18 (q), 31.61 (q), 31.69 (q), 45.37 (t), 55.72 (s), 65.58 (s), 73.16 (d), 128.03 (d), 128.88 (2 x d), 129.06 (2 x d), 136.53 (s), 175.09 (s);  $m/z$  (EI) 312 [ $(\text{MH}^{81}\text{Br})^+$ , 97%], 310 [ $(\text{MH}^{79}\text{Br})^+$ , 100%], 230 (86), 178 (32), 142 (36), 91 (100); (Found:  $\text{MH}^+$ , 310.0772.  $\text{C}_{15}\text{H}_{20}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 310.0779).

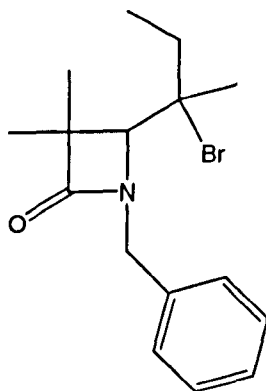
**6.4.7.6 1-(2-Bromo-benzyl)-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (136)**



2-Bromo-*N*-(2-bromo-benzyl)-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**129**) (100 mg, 0.23 mmol) was reacted as described above (6.4.7) to furnish 1-(2-bromo-benzyl)-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (**136**) (98 mg, 98%) as a colourless oil.

$\nu_{\max}$  (film) / $\text{cm}^{-1}$  2854, 1728, 1640, 1568, 1441, 1390, 1288, 1181, 1109, 1030, 835, 751;  
 $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.35 (3H, s,  $\text{CH}_3$ ), 1.51 (3H, s,  $\text{CH}_3$ ), 1.49-1.72 (6H, m,  $\text{CH}_2$ ),  
 1.80-1.88 (2H, m,  $\text{CH}_2$ ), 2.04-2.10 (2H, m,  $\text{CH}_2$ ), 3.57 (1H, s,  $\text{NCH}$ ), 4.45 (1H, d,  $J$  16.5,  
 $\text{NCHH}$ ), 4.77 (1H, d,  $J$  16.5,  $\text{NCHH}$ ), , 7.05-7.11 (1H, m, H-5), 7.23-7.28 (2H, m, H-4  
 and H-6), 7.48 (1H, d,  $J$  7.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 17.46 (q), 20.86 (2 x t), 21.50  
 (2 x t), 23.91 (q), 23.93 (t), 44.19 (t), 54.57 (s), 72.29 (s), 72.67 (d), 121.95 (s), 126.64  
 (d), 128.06 (d), 128.35 (d), 132.09 (d), 134.09 (s), 174.15 (s);  $m/z$  (EI) 432 [(MH- $^{81}\text{Br}$   
 $^{81}\text{Br}$ ) $^+$ , 76%], 430 [(MH- $^{81}\text{Br}$   $^{79}\text{Br}$ ) $^+$ , 100%], 428 [(MH- $^{79}\text{Br}$   $^{79}\text{Br}$ ) $^+$ , 56%], 385 (53), 350  
 (52), 169 (36), 83 (100).

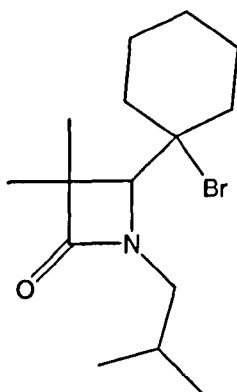
#### 6.4.7.7 1-Benzyl-4-(1-bromo-1-methyl-propyl)-3,3-dimethyl-azetidin-2-one (142)



*N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-but-1-enyl)-propionamide (**124**) (100 mg, 0.28 mmol) was reacted as described above (6.4.7) to afford 1-benzyl-4-(1-bromo-1-methyl-propyl)-3,3-dimethyl-azetidin-2-one (**142**) (95 mg, 95%) as a colourless oily mixture of 2 isomers ratio (2:1).

$\nu_{\max}$  (film) / $\text{cm}^{-1}$  mixture 2934, 1695, 1602, 1579, 1457, 1438, 1377, 1287, 743, 710;  
 $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) *major isomer* 0.98 (3H, t,  $J$  7.0,  $\text{CH}_2\text{CH}_3$ ), 1.18 (3H, s,  $\text{CH}_3$ ), 1.27 (3H, s,  $\text{CH}_3$ ), 1.68 (3H, s,  $\text{CBrCH}_3$ ), 1.83 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 3.68 (1H, s,  $\text{NCH}$ ), 4.24 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 4.87 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 7.23-7.30 (5H, m, aromatic H);  
*minor isomer* 0.80 (3H, t,  $J$  7.0,  $\text{CH}_2\text{CH}_3$ ), 1.19 (3H, s,  $\text{CH}_3$ ), 1.36 (3H, s,  $\text{CH}_3$ ), 1.62 (3H, s,  $\text{CBrCH}_3$ ), 1.71 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 3.55 (1H, s,  $\text{NCH}$ ), 4.05 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 4.86 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 7.17-7.25 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) mixture 8.92 (q), 9.1 (q), 17.13 (q), 17.17 (q), 23.11 (q), 23.35 (q), 26.13 (q), 26.39 (q), 34.42 (t), 34.75 (t), 43.82 (t), 44.11 (t), 54.11 (s), 54.45 (t), 70.45 (s), 70.93 (d), 71.11 (d), 72.26 (s), 126.51 (d), 126.65 (d), 127.32 (2 x d), 127.57 (2 x d), 127.58 (2 x d), 127.69 (2 x d), 135.01 (s), 135.34 (s), 173.48 (s), 173.78 (s);  $m/z$  (EI) mixture 326 [(MH- $^{81}\text{Br}$ ) $^+$ , 94%], 324 [(MH- $^{79}\text{Br}$ ) $^+$ , 100%], 214 (86), 91 (100).

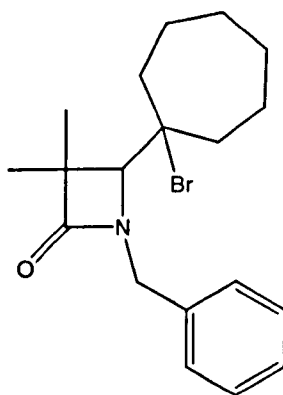
#### 6.4.7.8 4-(1-Bromo-cyclohexyl)-1-isobutyl-3,3-dimethyl-azetidin-2-one (135)



2-Bromo-*N*-cyclohexylidenemethyl-*N*-isobutyl-2-methyl-propionamide (**128**) (100 mg, 0.31 mmol) was reacted as described above (6.4.7) to furnish 4-(1-bromo-cyclohexyl)-1-isobutyl-3,3-dimethyl-azetidin-2-one (**135**) (97 mg, 97%) as a colourless oil.

$\nu_{\max}$  (neat) /cm<sup>-1</sup> 2932, 1642, 1464, 1380, 1288, 1079, 837, 746;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 0.86 (3H, d, *J* 7.0, CHCH<sub>3</sub>CH<sub>3</sub>), 0.87 (3H, d, *J* 7.0, CHCH<sub>3</sub>CH<sub>3</sub>), 1.29 (3H, s, CH<sub>3</sub>), 1.38 (3H, s, CH<sub>3</sub>), 1.43-1.89 (8H, m, CH<sub>2</sub>), 1.92-2.15 (3H, m, CH<sub>2</sub> and NCH<sub>2</sub>CH), 2.92 (1H, dd, *J* 14.0, *J* 5.5, NCHHCH), 3.26 (1H, dd, *J* 14.0, *J* 5.5, NCHHCH), 3.66 (1H, s, NCH);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 17.54 (q), 18.95 (q), 19.34 (q), 20.97 (2 x t), 21.65 (2 x t), 24.13 (t), 24.30 (q), 28.68 (d), 36.17 (s), 47.92 (t), 54.08 (s), 72.73 (d), 173.54 (s); *m/z* (CI) 318 [(MH-<sup>81</sup>Br)<sup>+</sup>, 73%], 316 [(MH-<sup>79</sup>Br)<sup>+</sup>, 76%], 287 (32), 235 (94), 194 (38).

#### 6.4.7.9 1-Benzyl-4-(1-bromo-cycloheptyl)3,3-dimethyl-azetidin-2-one (**144**)



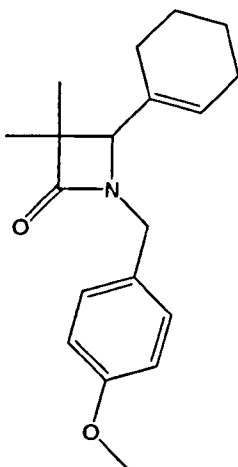
*N*-Benzyl-2-bromo-*N*-cycloheptylidenemethyl-2-methyl-propionamide (**123**) (100 mg, 0.27 mmol) was reacted as described above (6.4.7) to furnish 1-benzyl-4-(1-bromo-cycloheptyl)3,3-dimethyl-azetidin-2-one (**144**) (96 mg, 96%) as a colourless oil.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 2934, 1732, 1643, 1519, 1416, 1265, 926, 701;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.23 (3H, s, *CH*<sub>3</sub>), 1.39 (3H, s, *CH*<sub>3</sub>), 1.41-2.14 (10H, m, *CH*<sub>2</sub>), 2.20-2.36 (2H, m, *CH*<sub>2</sub>), 3.42 (1H, s, *NCH*), 4.09 (1H, d, *J* 15.0, *NCHH*), 4.93 (1H, d, *J* 15.0, *NCHH*), 7.19-7.29 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 16.20 (q), 21.48 (q), 23.59 (t), 25.25 (t), 26.04 (t), 26.95 (t), 28.67 (t), 30.04 (t), 39.04 (s), 43.67 (t), 53.77 (s), 67.43 (d), 127.69 (2 x d), 127.74 (2 x d), 128.46 (d), 137.86 (s), 173.85 (s); *m/z* (EI) 366 [(MH-<sup>81</sup>Br)<sup>+</sup>, 87%], 364 [(MH-<sup>79</sup>Br)<sup>+</sup>, 91%], 284 (52), 271 (23), 184 (14), 91 (100).

#### 6.4.8 General procedure for the elimination of tertiary-bromo- $\beta$ -lactams.

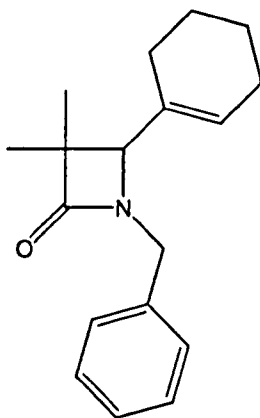
To a stirred solution of the tertiary-bromo- $\beta$ -lactam in dichloromethane under a nitrogen atmosphere was added DBU (1 eq.). The resulting mixture was stirred for 12 hours at room temperature. The mixture was then washed with a 5% aqueous solution of HCl followed by a saturated solution of sodium chloride. The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield the corresponding alkene.

## 6.4.8.1 4-Cyclohex-1-enyl-1-(4-methoxy-benzyl)-3,3-dimethyl-azetidin-2-one (138)



4-(1-Bromo-cyclohexyl)-1-(4-methoxy-benzyl)-3,3-dimethyl-azetidin-2-one (134) (30 mg, 0.08 mmol) was reacted as described above (6.4.8) to furnish 4-cyclohex-1-enyl-1-(4-methoxy-benzyl)-3,3-dimethyl-azetidin-2-one (138) (23 mg, 98%) as a pale yellow oil.  $\nu_{\max}$  (neat) / $\text{cm}^{-1}$  2932, 2842, 1719, 1672, 1438, 1024, 836, 753;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 0.98 (3H, s,  $\text{CH}_3$ ), 1.17 (3H, s,  $\text{CH}_3$ ), 1.41-1.74 (6H, m,  $\text{CH}_2$ ), 1.98-2.05 (2H, m,  $\text{CH}_2$ ), 3.25 (1H, s,  $\text{NCH}$ ), 3.72 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 3.73 (3H, s,  $\text{OCH}_3$ ), 4.69 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 5.50 (1H, br s,  $\text{C=CH}$ ), 6.78 (2H, d,  $J$  8.0, aromatic H), 7.09 (2H, d,  $J$  8.0, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 17.13 (q), 22.75 (t), 22.80 (q), 25.21 (t), 25.41 (t), 27.70 (t), 44.16 (t), 55.09 (s), 55.64 (q), 66.44 (d), 114.40 (2 x d), 123.63 (d), 128.63 (s), 130.07 (2 x d), 133.26 (s), 159.35 (s), 174.67 (s);  $m/z$  (EI) 300 ( $\text{MH}^+$ , 60%), 136 (71), 121 (89), 81 (12); (Found:  $\text{MH}^+$ , 300.1959.  $\text{C}_{19}\text{H}_{24}\text{NO}_2$  requires  $\text{MH}^+$ , 300.1967).

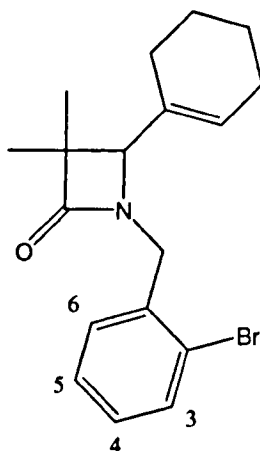


6.4.8.2 1-Benzyl-4-cyclohex-1-enyl-3,3-dimethyl-azetidin-2-one (**137**)

1-Benzyl-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (**133**) (100 mg, 0.28 mmol) was reacted as described above (6.4.8) to afford 1-benzyl-4-cyclohex-1-enyl-3,3-dimethyl-azetidin-2-one (**137**) (71 mg, 94%) as a colourless oil.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  2929, 1727, 1642, 1464, 1440, 1268, 1027, 845, 751;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 0.98 (3H, s,  $\text{CH}_3$ ), 1.19 (3H, s,  $\text{CH}_3$ ), 1.46-1.75 (6H, m,  $\text{CH}_2$ ), 1.97-2.04 (2H, m,  $\text{CH}_2$ ), 3.28 (1H, s,  $\text{NCH}$ ), 3.79 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 4.74 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 5.48 (1H, br s,  $\text{C=CH}$ ), 7.11-7.27 (5H, m, aromatic H);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ) 17.13 (q), 22.73 (t), 22.79 (t), 22.85 (q), 25.21 (t), 27.70 (t), 44.77 (t), 44.25 (s), 66.69 (d), 123.74 (d), 127.94 (d), 128.75 (2 x d), 129.09 (2 x d), 133.16 (s), 164.21 (s), 174.81 (s);  $m/z$  (EI) 270 ( $\text{MH}^+$ , 100%), 200 (34), 136 (100), 91 (90); (Found:  $\text{MH}^+$ , 270.1862.  $\text{C}_{18}\text{H}_{23}\text{NO}$  requires  $\text{MH}^+$ , 270.1859).

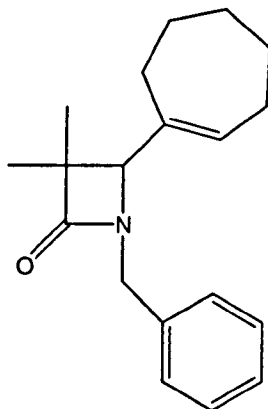
## 6.4.8.3 1-(2-Bromo-benzyl)-4-cyclohex-1-enyl-3,3-dimethyl-azetidin-2-one (139)



1-(2-Bromo-benzyl)-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (**136**) (30 mg, 0.08 mmol) was reacted as described above (6.4.8) to furnish 1-(2-bromo-benzyl)-4-cyclohex-1-enyl-3,3-dimethyl-azetidin-2-one (**139**) (23 mg, 97%) as a colourless oil.

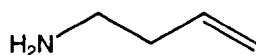
$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  3062, 2929, 1728, 1640, 1441, 1366, 1281, 1109, 752;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 0.99 (3H, s,  $\text{CH}_3$ ), 1.22 (3H, s,  $\text{CH}_3$ ), 1.41-1.62 (6H, m,  $\text{CH}_2$ ), 1.95-2.04 (2H, m,  $\text{CH}_2$ ), 3.30 (1H, s,  $\text{NCH}$ ), 4.10 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 4.73 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 5.49 (1H, br s,  $\text{C=CH}$ ), 7.05-7.11 (1H, m, H-5), 7.18-7.24 (2H, m, H-4 and H-6), 7.47 (1H, d,  $J$  8.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 17.31 (q), 22.78 (2 x t), 23.10 (q), 25.25 (t), 27.80 (t), 45.03 (t), 55.33 (s), 67.47 (d), 123.88 (d), 124.22 (s), 128.10 (d), 129.67 (d), 131.11 (d), 133.31 (d), 133.51 (s), 135.58 (s), 174.59 (s);  $m/z$  (EI) 350 [ $(\text{MH}^{81}\text{Br})^+$ , 95%], 348 [ $(\text{MH}^{79}\text{Br})^+$ , 100%], 268 (33), 169 (21), 136 (100), 91 (16); (Found:  $\text{MH}^+$ , 348.0952.  $\text{C}_{18}\text{H}_{22}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 348.0961).

## 6.4.8.4 1-Benzyl-4-cyclohept-1-enyl-3,3-dimethyl-azetidin-2-one (229)



1-Benzyl-4-(1-bromo-cycloheptyl)3,3-dimethyl-azetidin-2-one (**144**) (50 mg, 0.14 mmol) was reacted as described above (6.4.8) to furnish 1-benzyl-4-cyclohept-1-enyl-3,3-dimethyl-azetidin-2-one (**229**) (0.16 mg, 94%) as a colourless oil.

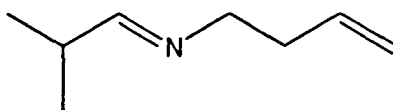
$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  2934, 1731, 1697, 1574, 1439, 1264, 786, 701;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 0.98 (3H, s,  $\text{CH}_3$ ), 1.22 (3H, s,  $\text{CH}_3$ ), 1.34-1.46 (4H, m,  $\text{CH}_2$ ), 1.63-1.70 (2H, m,  $\text{CH}_2$ ), 1.85-1.90 (2H, m,  $\text{CH}_2$ ), 2.08-2.14 (2H, m,  $\text{CH}_2$ ), 3.34 (1H, s,  $\text{NCH}$ ), 3.77 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 4.74 (1H, d,  $J$  15.0,  $\text{NCHH}$ ), 5.64 (1H, t,  $J$  6.5,  $\text{C=CH}$ ), 7.14-7.26 (5H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 13.12 (q), 21.45 (q), 25.27 (t), 26.09 (t), 27.26 (t), 30.91 (t), 31.31 (t), 43.36 (t), 53.93 (s), 67.10 (d), 126.55 (d), 127.66 (2 x d), 128.07 (2 x d), 128.40 (d), 134.97 (s), 138.24 (s), 173.28 (s);  $m/z$  (EI) 284 ( $\text{MH}^+$ , 85%), 187 (23), 91 (100); (Found:  $\text{MH}^+$ , 284.2003.  $\text{C}_{19}\text{H}_{25}\text{NO}$  requires  $\text{MH}^+$ , 284.2005).

6.4.9 But-3-enylamine (230)<sup>17</sup>

To a suspension of potassium phthalimide (4.5 g, 24.0 mmol) in DMF (50.0 ml) was added 4-bromo-1-butene (2.25 ml, 22.0 mmol) and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with water (50 ml) and then extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with a 10% aqueous solution of sodium hydroxide (2 x 30 ml.) and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure to furnish 2-but-3-enyl-isoindole-1,3-dione (2.74 g, 62%).  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 2.44 (2H, q,  $J$  7.0,  $\text{NCH}_2\text{CH}_2\text{CH}$ ), 3.75 (2H, t,  $J$  7.0,  $\text{NCH}_2\text{CH}_2$ ), 4.97-5.28 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.69-5.85 (1H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 7.65-7.72 (2H, m, aromatic H), 7.78-7.85 (2H, m, aromatic H);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 33.23 (t), 37.69 (t), 117.95 (t), 123.59 (2 x d), 132.45 (2 x s), 134.28 (2 x d), 134.85 (d), 168.74 (2 x s). To a solution of 2-but-3-enyl-isoindole-1,3-dione (2.0 g, 9.95 mmol) in diethyl ether (30 ml.) was added hydrazine hydrate (0.92 ml, 29.85 mmol) and the mixture stirred at room temperature overnight. The mixture was diluted with water (20 ml.) and then added to an excess of concentrated hydrochloric acid. The resulting precipitate was filtered off and the filtrate extracted with diethyl ether (3 x 15 ml.). The aqueous phase was then concentrated under reduced pressure to yield but-3-enylamine as the hydrochloride salt. Spectral details match those previously reported.<sup>17</sup>

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 2.21 (2H, app dq,  $J$  6.5,  $J$  1.5,  $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 2.74 (2H, t,  $J$  6.5,  $\text{NH}_2\text{CH}_2\text{CH}_2$ ), 4.85 (2H, br,  $\text{NH}_2$ ), 5.04-5.12 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.68-5.84 (1H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 38.23 (t), 41.42 (t), 117.15 (t), 136.43 (d).

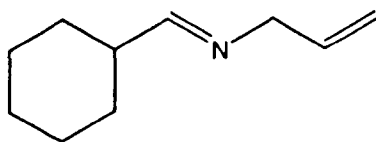
#### 6.4.10 But-3-enyl-isobutylidene-amine (231)



Isobutylaldehyde (1.02 ml, 11.0 mmol) and but-3-enylamine (0.8 g, 11.0 mmol) were reacted as described previously (6.4.1) to afford but-3-enyl-isobutylidene-amine (**231**) as a colourless oil which was used without further purification (1.32 g, 96%).

$\nu_{\text{max}}$  (neat)  $/\text{cm}^{-1}$  3027, 2948, 1650, 1452, 1372, 1029, 728;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 0.94 (3H, d,  $J$  7.0,  $\text{CHCH}_3\text{CH}_3$ ), 1.04 (3H, app dd,  $J$  7.0,  $J$  1.0,  $\text{CHCH}_3\text{CH}_3$ ), 2.23 (2H, q,  $J$  7.0,  $\text{NCH}_2\text{CH}_2\text{CH}$ ), 2.26-2.30 (1H, m,  $\text{CHCH}_3\text{CH}_3$ ), 3.34 (2H, t,  $J$  7.0,  $\text{NCH}_2\text{CH}_2$ ), 4.91-5.05 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.62-5.76 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.42 (1H, dd,  $J$  5.5,  $J$  1.0,  $\text{N}=\text{CHCH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 19.82 (q), 19.92 (q), 34.38 (d), 35.51 (t), 60.90 (t), 116.44 (t), 136.60 (d), 170.69 (d);  $m/z$  (EI) 126 ( $\text{MH}^+$ , 64%), 84 (19), 63 (9).

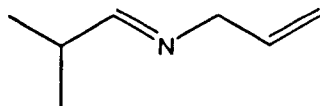
#### 6.4.11 Allyl-cyclohexylmethlene-amine (232)



Cyclohexanecarboxaldehyde (2.7 ml, 22.0 mmol) and allylamine (1.67 ml, 22.0 mmol) were reacted as described previously (6.4.1) to furnish allyl-cyclohexylmethlene-amine (**232**) as a colourless oil which was used without further purification (3.1 g, 91%).

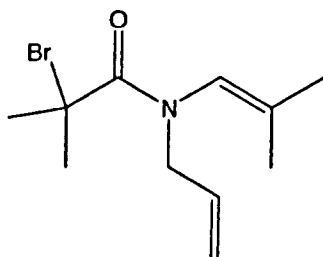
$\nu_{\max}$  (film) / $\text{cm}^{-1}$  2954, 2866, 1650, 1365, 1158, 731;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.08-1.32 (5H, m,  $\text{CH}_2$ ), 1.56-1.77 (5H, m,  $\text{CH}_2$ ), 2.04-2.18 (1H, m,  $\text{N}=\text{CHCH}$ ), 3.90 (2H, d,  $J$  6.5,  $\text{NCH}_2\text{CH}$ ), 4.98-5.22 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.82-5.97 (1H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 7.45 (1H, d,  $J$  6.0,  $\text{N}=\text{CHCH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 25.34 (2 x t), 25.83 (t), 29.78 (2 x t), 43.88 (d), 63.71 (t), 115.82 (t), 136.56 (d), 170.43 (d).

#### 6.4.12 Allyl-isobutylidene-amine (**233**)<sup>18</sup>



Isobutylaldehyde (2.51 ml, 27.7 mmol) and allylamine (2.07 ml, 27.7 mmol) were reacted as described previously (6.4.1) to furnish allyl-isobutylidene-amine (**233**) as a colourless oil which was used without further purification (2.7 g, 89%). Spectral details match those previously reported.<sup>18</sup>

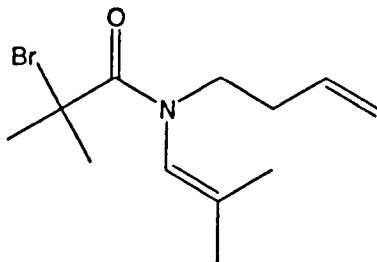
$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.12 (6H, d,  $J$  7.0,  $\text{CHCH}_3\text{CH}_3$ ), 2.41-2.52 (1H, m,  $\text{CHCH}_3\text{CH}_3$ ), 3.99 (2H, dt,  $J$  5.0,  $J$  1.0,  $\text{NCH}_2\text{CH}$ ), 5.07-5.19 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.92-6.04 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.56 (1H, app dt,  $J$  5.0,  $J$  1.0,  $\text{N}=\text{CHCH}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 19.67 (2 x q), 34.48 (d), 63.59 (t), 115.92 (t), 136.54 (d), 171.31 (d).

6.4.13 *N*-Allyl-2-bromo-2-methyl-*N*-(2-methyl-propenyl)-propionamide (150)

To a solution of allyl-isobutylidene-amine (**233**) (1.95 g, 17.0 mmol) was added 2-bromo-2-methylpropionyl bromide (2.17 ml, 17.0 mmol). Purification by flash column chromatography eluting with 5:2 petroleum ether:ethyl acetate afforded *N*-allyl-2-bromo-2-methyl-*N*-(2-methyl-propenyl)-propionamide (**150**) (2.5 g, 57%) as a pale yellow oil.

$\nu_{\text{max}}$  (film) / $\text{cm}^{-1}$  2929, 2852, 1737, 1641, 1462, 1179, 1002, 728;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.64 (3H, d,  $J$  1.0,  $\text{CH}=\text{CCH}_3\text{CH}_3$ ), 1.76 (3H, d,  $J$  1.0,  $\text{CH}=\text{CCH}_3\text{CH}_3$ ), 1.93 (6H, s,  $\text{C}(\text{Br})\text{CH}_3\text{CH}_3$ ), 4.06 (2H, br d,  $J$  5.5,  $\text{NCH}_2\text{CH}$ ), 5.11-5.20 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.76-5.89 (1H, m,  $\text{CH}=\text{CH}_2$ ), 6.41 (1H, br s,  $\text{NCH}=\text{C}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 14.59 (q), 18.61 (q), 32.35 (2 x q), 54.50 (t), 58.60 (s), 116.90 (t), 126.22 (d), 132.98 (d), 134.91 (s), 170.70 (s);  $m/z$  (CI) 262 [ $(\text{MH}^{+81}\text{Br})^+$ , 64%], 260 [ $(\text{MH}^{+79}\text{Br})^+$ , 64%], 178 (72), 138 (32); (Found:  $\text{MH}^+$ , 260.0651.  $\text{C}_{11}\text{H}_{18}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 260.0652).

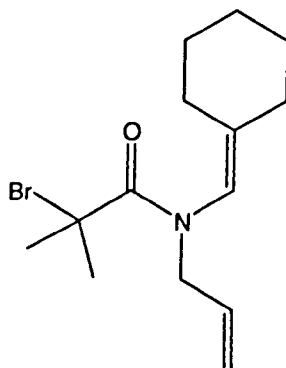
**6.4.14 2-Bromo-*N*-but-3-enyl-2-methyl-*N*-(2-methyl-propenyl)-propionamide**  
**(151)**



To a solution of but-3-enyl-isobutylidene-amine (**231**) (0.45 g, 3.6 mmol) was added 2-bromo-2-methylpropionyl bromide (0.57 ml, 3.6 mmol). Purification by flash column chromatography eluting with 5:2 petroleum ether:ethyl acetate furnished 2-bromo-*N*-but-3-enyl-2-methyl-*N*-(2-methyl-propenyl)-propionamide (**151**) (0.52 g, 53%) as a colourless oil.

$\nu_{\max}$  (film) / $\text{cm}^{-1}$  2976, 1737, 1641, 1447, 1393, 1294, 1185, 1108, 914, 833;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.64 (3H, d,  $J$  1.0,  $\text{CH}=\text{CCH}_3\text{CH}_3$ ), 1.85 (3H, d,  $J$  1.0,  $\text{CH}=\text{CCH}_3\text{CH}_3$ ), 1.97 (6H, s,  $\text{C}(\text{Br})\text{CH}_3\text{CH}_3$ ), 2.35 (2H, q,  $J$  7.5,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 3.53 (2H, t,  $J$  7.5,  $\text{NCH}_2\text{CH}_2$ ), 4.99-5.11 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.69-5.84 (1H, m,  $\text{CH}=\text{CH}_2$ ), 6.41 (1H, br s,  $\text{NCH}=\text{C}$ );  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ) 15.62 (q), 19.69 (q), 29.32 (2 x q), 34.74 (t), 51.04 (t), 58.45 (s), 116.23 (t), 124.39 (d), 134.12 (d), 129.87 (s), 170.42 (s);  $m/z$  (EI) 276 [(MH- $^{81}\text{Br}$ ) $^+$ , 44%], 274 [(MH- $^{79}\text{Br}$ ) $^+$ , 42%], 193 (65), 138 (26), 55 (19).

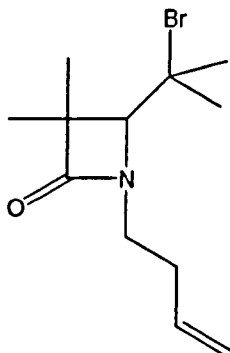


6.4.15 *N*-Allyl-2-bromo-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**149**)

To a solution of allyl-cyclohexylmethlene-amine (**232**) (3.0 g, 19.0 mmol) was added 2-bromo-2-methylpropionyl bromide (2.45 ml, 19.0 mmol). Purification by flash column chromatography eluting with 9:1 petroleum ether:ethyl acetate furnished *N*-allyl-2-bromo-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**149**) (2.96 g, 52%) as a colourless oil.

$\nu_{\text{max}}$  (film) / $\text{cm}^{-1}$  2930, 1738, 1639, 1448, 1365, 1180, 1109, 836, 751;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.52-1.65 (6H, m,  $\text{CH}_2$ ), 2.03 (6H, s,  $\text{C}(\text{Br})\text{CH}_3\text{CH}_3$ ), 2.11-2.18 (4H, m,  $\text{CH}_2$ ), 4.05 (2H, d,  $J$  5.5,  $\text{NCH}_2\text{CH}$ ), 5.11-5.20 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.77-5.90 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.28 (1H, br s,  $\text{NCH}=\text{C}$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 26.49 (t), 26.62 (t), 27.87 (t), 28.88 (t), 32.61 (2 x q), 33.20 (t), 55.18 (t), 58.83 (s), 116.94 (t), 123.22 (d), 133.03 (d), 141.19 (s), 170.69 (s);  $m/z$  (EI) 302 [ $(\text{MH}^{81}\text{Br})^+$ , 64%], 300 [ $(\text{MH}^{79}\text{Br})^+$ , 67%], 219 (78), 163 (31), 136 (17); (Found:  $\text{MH}^+$ , 300.0969.  $\text{C}_{14}\text{H}_{22}^{79}\text{BrNO}$  requires  $\text{MH}^+$ , 300.0964).

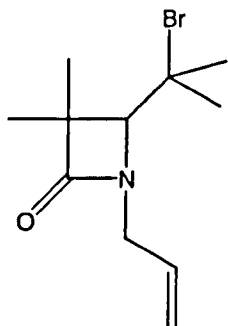
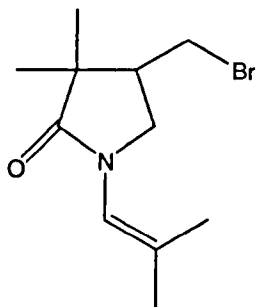
## 6.4.16 4-(1-Bromo-1-methyl-ethyl)-1-but-3-enyl-3,3-dimethyl-azetidin-2-one (156)



2-Bromo-*N*-but-3-enyl-2-methyl-*N*-(2-methyl-propenyl)-propionamide (**151**) (100 mg, 0.36 mmol) was reacted as described previously (6.4.7) to afford 4-(1-bromo-1-methyl-ethyl)-1-but-3-enyl-3,3-dimethyl-azetidin-2-one (**156**) (89 mg, 89%) as a colourless oil.

$\nu_{\max}$  (film) /cm<sup>-1</sup> 3368, 2975, 1731, 1651, 1530, 1461, 1412, 1284, 1170, 920, 739;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.24 (3H, s, C(Br)CH<sub>3</sub>CH<sub>3</sub>), 1.25 (3H, s, C(Br)CH<sub>3</sub>CH<sub>3</sub>), 1.82 (6H, s, CCH<sub>3</sub>CH<sub>3</sub>), 2.39 (2H, app dq, *J* 7.5, *J* 1.0, CH<sub>2</sub>CH<sub>2</sub>CH), 3.15-3.23 (1H, m, NCHHCH<sub>2</sub>), 3.59-3.69 (1H, m, NCHHCH<sub>2</sub>), 3.78 (1H, s, NCH), 4.97-5.11 (2H, m, CH=CH<sub>2</sub>), 5.66-5.75 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 16.95 (q), 25.27 (q), 30.59 (q), 31.80 (q), 32.35 (t), 39.56 (t), 55.51 (s), 66.48 (s), 73.07 (d), 117.78 (t), 135.44 (d), 174.77 (s); *m/z* (EI) 276 [(MH-<sup>81</sup>Br)<sup>+</sup>, 86%], 274 [(MH-<sup>79</sup>Br)<sup>+</sup>, 90%], 193 (44), 152 (68), 58 (23); (Found: MH<sup>+</sup>, 274.0811. C<sub>12</sub>H<sub>20</sub><sup>79</sup>BrNO requires MH<sup>+</sup>, 274.0807).

**6.4.17 Cyclisation of *N*-Allyl-2-bromo-2-methyl-*N*-(2-methyl-propenyl)-propionamide (150)**

**155****154**

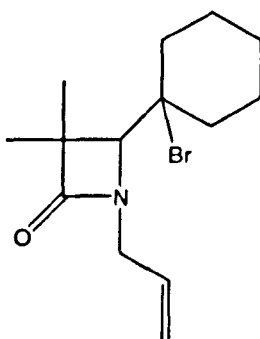
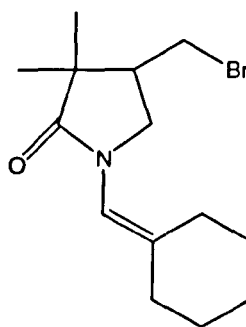
*N*-Allyl-2-bromo-2-methyl-*N*-(2-methyl-propenyl)-propionamide (**150**) (100 mg, 0.38 mmol) was reacted as described previously (6.4.7) to furnish an inseparable (3:2) mixture of 1-allyl-4-(bromo-1-methyl-ethyl)-3,3-dimethyl-azetidin-2-one (**155**) and 4-bromomethyl-3,3-dimethyl-1-(2-methyl-propenyl)-pyrrolidin-2-one (**154**) (92 mg) in the form of a colourless oil.

$\nu_{\max}$  (film) /cm<sup>-1</sup> mixture 3273, 2924, 1745, 1658, 1462, 1369, 1173, 1079, 817;

Discernible data for 1-allyl-4-(bromo-1-methyl-ethyl)-3,3-dimethyl-azetidin-2-one (**155**),  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.26 (3H, s, CCH<sub>3</sub>CH<sub>3</sub>), 1.30 (3H, s, CCH<sub>3</sub>CH<sub>3</sub>), 1.80 (6H, s, C(Br)CH<sub>3</sub>CH<sub>3</sub>), 3.69 (1H, s, NCH), 3.70 (1H, m, NCHH), 4.19 (1H, ddt, *J* 15.5, *J* 5.5, *J* 1.1, NCHH) 5.16-5.27 (2H, m, CH=CH<sub>2</sub>), 5.69-5.75 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>); discernible data for and 4-bromomethyl-3,3-dimethyl-1-(2-methyl-propenyl)-pyrrolidin-2-one (**154**),  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.26 (3H, s, CCH<sub>3</sub>CH<sub>3</sub>), 1.30 (3H, s, CCH<sub>3</sub>CH<sub>3</sub>), 1.61 (3H, d, *J* 1.5, CH=CCH<sub>3</sub>CH<sub>3</sub>), 1.68 (3H, d, *J* 1.5, CH=CH<sub>3</sub>CH<sub>3</sub>), 2.39-2.48 (1H, m, NCH<sub>2</sub>CH), 3.18-3.30 (1H, m, NCHH), 3.45 (1H, dd, *J* 10.0, *J* 4.5, NCHH), 3.67-3.74 (2H, m,

CHCH<sub>2</sub>Br), 5.77-5.82 (1H, m, NCH=C);  $\delta_c$ (75.5 MHz, CDCl<sub>3</sub>) *mixture* 16.84 (2 x q), 22.09 (2 x q), 28.68 (t), 29.83 (t), 30.17 (2 x q), 30.26 (q), 30.39 (q), 39.24 (s), 39.89 (d), 41.34 (s), 42.64 (t), 49.36 (s), 72.22 (d), 104.63 (s), 116.23 (d), 117.78 (t), 130.89 (d), 179.03 (s), 182.79 (s).

#### 6.4.18 Cyclisation of *N*-allyl-2-bromo-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**149**)

**152****153**

*N*-Allyl-2-bromo-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**149**) (100 mg, 0.33 mmol) was reacted as described previously (6.4.7) to furnish an inseparable (1:1.75) mixture of 1-allyl-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (**152**) and 4-bromomethyl-1-cyclohexylidenemethyl-3,3-dimethyl-pyrrolidin-2-one (**153**) (96 mg) in the form of a colourless oil.

$\nu_{\max}$  (film) /cm<sup>-1</sup> *mixture* 3394, 2929, 1734, 1651, 1461, 1414, 1371, 1170, 1038, 920, 739; Discernible data for and 4-bromomethyl-1-cyclohexylidenemethyl-3,3-dimethyl-pyrrolidin-2-one (**153**),  $\delta_H$ (300 MHz, CDCl<sub>3</sub>) 1.17 (3H, s, CCH<sub>3</sub>CH<sub>3</sub>), 1.18 (3H, s, CCH<sub>3</sub>CH<sub>3</sub>), 2.37-2.47 (1H, m, CHCH<sub>2</sub>Br), 3.19-3.29 (2H, m, CHCH<sub>2</sub>Br), 3.46 (1H, dd, *J*

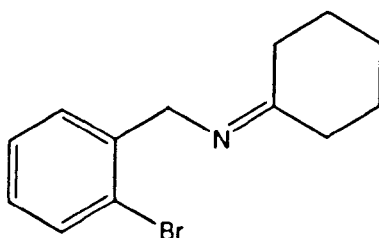
10.0, *J* 4.5, *NCHH*), 3.62 (1H, m, *NCHH*), 5.80 (1H, s, *NCH=C*); discernible data for 1-allyl-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidin-2-one (**152**),  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.27 (3H, s,  $\text{CCH}_3\text{CH}_3$ ), 1.49 (3H, s,  $\text{CCH}_3\text{CH}_3$ ), 3.61 (1H, s, *NCH*), 3.64 (1H, m, *NCHH*), 4.20 (1H, ddt, *J* 15.5, *J* 5.0, *J* 1.5, *NCHH*), 5.15-5.20 (2H, m,  $\text{CH=CH}_2$ ), 5.67-5.75 (1H, m,  $\text{CH}_2\text{CH=CH}_2$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) *mixture* 18.75 (q), 18.86 (q), 22.37 (2 x t), 23.02 (t), 24.62 (q), 25.36 (q), 25.46 (t), 26.74 (t), 27.59 (t), 28.46 (t), 29.38 (2 x t), 31.80 (2 x t), 34.31 (t), 37.94 (s), 44.06 (s), 46.93 (d), 52.24 (t), 55.84 (s), 73.61 (d), 116.40 (d), 119.07 (t), 132.54 (d), 136.28 (s), 178.45 (s), 182.47 (s).

## 6.5 Experimental for chapter 5

### 6.5.1 General procedure for the preparation of imines.

A solution of primary amine (1 eq.) and cyclohexanone (1 eq.) in toluene were heated at reflux in a Dean-Stark apparatus with azeotropic removal of water for 4 hours. The solvent was then removed under reduced pressure to yield the imine.

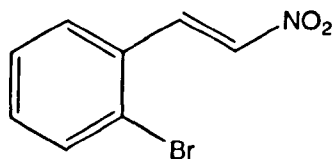
#### 6.5.1.1 (2-Bromo-benzyl)-cyclohexylidene-amine (190)



Condensation of *o*-bromobenzylamine (4.0g, 21.0 mmol) and cyclohexanone (2.06 g, 21.0 mmol) as described above (6.5.1) afforded (2-bromo-benzyl)-cyclohexylidene-amine (**190**) (5.05 g, 91%) as a pale yellow oil which was used without further purification.

$\nu_{\max}$  (neat) /cm<sup>-1</sup> 2934, 2859, 1716, 1663, 1568, 1464, 1441, 1347, 1026;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.42-2.08 (8H, m, CH<sub>2</sub>), 2.23-2.40 (2H, m, CH<sub>2</sub>), 4.50 (2H, s, NCH<sub>2</sub>), 6.98-7.09 (1H, m, aromatic H), 7.12-7.24 (2H, m, aromatic H), 7.46 (1H, d, *J* 7.0, C(Br)CH); *m/z* (CI) 268 [(MH-<sup>81</sup>Br)<sup>+</sup>, 30%], 266 [(M-<sup>79</sup>Br)<sup>+</sup>, 29%], 186 (30).

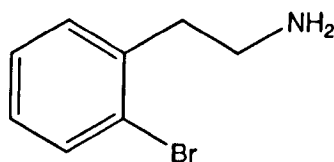
### 6.5.2 1-Bromo-2-(2-nitro-vinyl)-benzene (**200**)<sup>16</sup>



To a solution of 2-bromobenzaldehyde (5.0 ml, 43.2 mmol) and nitromethane (2.34 ml, 43.2 mmol) in methanol (10 ml) was added an aqueous solution of sodium hydroxide (1.8 ml, 25 M). A white precipitate formed immediately and the resulting mixture was stirred for one hour at room temperature. The precipitate was dissolved by the addition of water (100 ml) and the aqueous solution added to an excess of hydrochloric acid to deposit the crude product. Recrystallisation from ethanol afforded 1-bromo-2-(2-nitro-vinyl)-benzene (**200**) (3.48g, 73%) as pale yellow pillars; m.p. 89-92°C. Spectral details match those previously reported.<sup>16</sup>

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  1634, 1584, 1502, 1466, 1340, 1286, 1025, 953, 760, 599;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 7.24-7.36 (2H, m, aromatic H), 7.47 (1H, d,  $J$  12.0,  $\text{CH}=\text{CHNO}_2$ ), 7.47-7.53 (1H, m, aromatic H), 7.62 (1H, dd,  $J$  7.5,  $J$  1.5,  $\text{C}(\text{Br})\text{CHCH}$ ), 8.34 (1H, d,  $J$  12.0,  $\text{CH}=\text{CHNO}_2$ );  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 126.74 (s), 128.50 (d), 128.88 (d), 130.73 (s), 132.98 (d), 133.56 (d), 137.98 (d), 139.23 (d);  $m/z$  (EI) 229 [ $(\text{M}-^{81}\text{Br})^+$ , 29%], 227 [ $(\text{M}-^{79}\text{Br})^+$ , 31%], 148 (48), 118 (100), 75 (52).

### 6.5.3 2-(2-Bromo-phenyl)-ethylamine (201)<sup>16</sup>

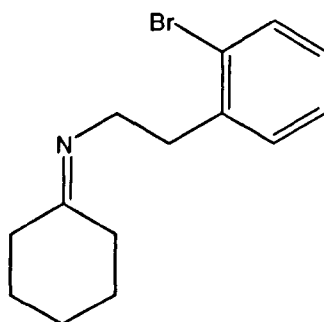


To a suspension of  $\text{LiAlH}_4$  (0.52 g, 14.1 mmol) in ether (20 ml) under an atmosphere of nitrogen was slowly added a solution of *o*-bromo- $\beta$ -nitrostyrene (200) (0.8 g, 3.52 mmol) in ether (10 ml) with ice cooling. The mixture was stirred at room temperature for 30 minutes then the excess  $\text{LiAlH}_4$  was carefully destroyed by addition of wet ether and water. The mixture was then filtered through a celite pad, the organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to furnish 2-(2-bromo-phenyl)-ethylamine (201) (0.67 g, 96%) as a pale yellow oil which was used without further purification. Spectral details match those previously reported.<sup>16</sup>

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  3383, 3062, 2919, 1568, 1471, 1440, 1025, 656;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.10-1.54 (2H, br s,  $\text{NH}_2$ ), 2.73-2.94 (4H, m,  $\text{CH}_2\text{CH}_2\text{NH}_2$ ), 6.92-6.98 (1H, m, aromatic

H), 7.03-7.22 (2H, m, aromatic H), 7.47 (1H, d,  $J$  7.5, C(Br)*CH*);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 39.94 (t), 41.76 (t), 124.45 (s), 127.21 (d), 127.74 (d), 130.69 (d), 132.71 (d), 148.09 (s);  $m/z$  (EI) 202 [ $(\text{MH}^{81}\text{Br})^+$ , 94%], 200 [ $(\text{MH}^{79}\text{Br})^+$ , 100%], 170 (3), 118 (8).

#### 6.5.1.2 [2-(2-Bromo-phenyl)-ethyl]-cyclohexylidene-amine (202)



Condensation of 2-(2-bromo-phenyl)-ethylamine (0.46 g, 2.3 mmol) and cyclohexanone (0.24 ml, 2.3 mmol) as described above (6.5.1) afforded [2-(2-bromo-phenyl)-ethyl]-cyclohexylidene-amine (**202**) (0.37 g, 58%) as a yellow oil which was used without further purification.

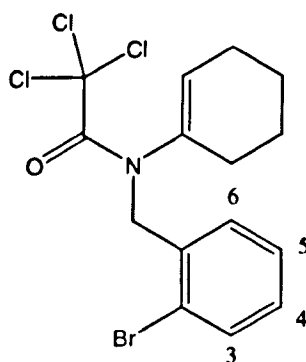
$\nu_{\text{max}}$  (neat)  $/\text{cm}^{-1}$  2928, 1724, 1657, 1442, 1029;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.45-2.11 (8H, m, *CH*<sub>2</sub>), 2.23-2.39 (2H, m, *CH*<sub>2</sub>), 3.03-3.08 (2H, m, *NCH*<sub>2</sub>*CH*<sub>2</sub>), 3.42-3.49 (2H, m, *NCH*<sub>2</sub>*CH*<sub>2</sub>), 7.02-7.10 (1H, m, aromatic H), 7.22-7.28 (2H, m, aromatic H), 7.54 (1H, d,  $J$  7.0, C(Br)*CH*);  $m/z$  (EI) 282 [ $(\text{MH}^{81}\text{Br})^+$ , 46%], 280 [ $(\text{MH}^{79}\text{Br})^+$ , 51%], 200 (13).



### 6.5.4 General procedure for the preparation of enamides.

To a solution of 2-bromo-2-methylpropionyl bromide (1.1 eq.) or trichloroacetyl chloride (1.1 eq.) in dry toluene under an atmosphere of nitrogen was added dropwise a solution of the imine (1.0 eq.) in dry toluene. After stirring for 1 hour at room temperature, the mixture was cooled to 0°C and triethylamine (3.0 eq.) added. Stirring was continued for 2 hours at room temperature, the mixture was then added to a saturated aqueous solution of  $\text{Na}_2\text{CO}_3$  and extracted with diethyl ether (3 x 20 ml.). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure.

#### 6.5.4.1 *N*-(2-Bromo-benzyl)-2,2,2-trichloro-*N*-cyclohex-1-enyl-acetamide (192)

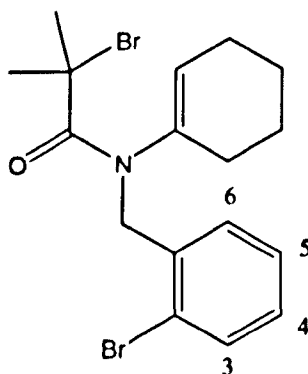


(2-Bromo-benzyl)-cyclohexylidene-amine (190) (2.0g, 7.5 mmol) and trichloroacetyl chloride (1.0 ml, 9.02 mmol) were reacted as described above (6.5.4). Purification by flash column chromatography eluting with 20:1 hexane:ethyl acetate furnished *N*-(2-

bromo-benzyl)-2,2,2-trichloro-*N*-cyclohex-1-enyl-acetamide (**192**) (1.17 g, 37%) as a pale yellow oil.

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  2938, 2862, 1667, 1441, 1351, 1391, 1218, 1027, 823;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.37-1.76 (6H, m,  $\text{CH}_2$ ), 1.87-2.09 (2H, m,  $\text{CH}_2$ ), 4.64 (1H, br,  $\text{NCHH}$ ), 5.07 (1H, br,  $\text{NCHH}$ ), 5.68 (1H, t,  $J$  4.0,  $\text{NC}=\text{CH}$ ), 7.11 (1H, dt,  $J$  7.5,  $J$  1.5, H-4), 7.29 (1H, dt,  $J$  7.5,  $J$  1.5, H-5), 7.42 (1H, dd,  $J$  7.5,  $J$  1.5, H-6), 7.50 (1H, dd,  $J$  7.5,  $J$  1.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 21.24 (t), 22.71 (t), 25.13 (t), 28.01 (t), 52.69 (t), 98.07 (s), 124.44 (s), 125.22 (d), 127.60 (d), 129.57 (d), 130.16 (d), 133.15 (d), 134.27 (s), 136.06 (s), 163.67 (s);  $m/z$  (EI) 412 [ $(\text{MH}^{81}\text{Br})^+$ , 68%], 410 [ $(\text{MH}^{79}\text{Br})^+$ , 32%], 342 (76), 306 (74), 260 (6), 226 (8), 186 (5).

#### 6.5.4.2 2-Bromo-*N*-(2-bromo-benzyl)-*N*-cyclohex-1-enyl-2-methyl-propionamide (**191**)

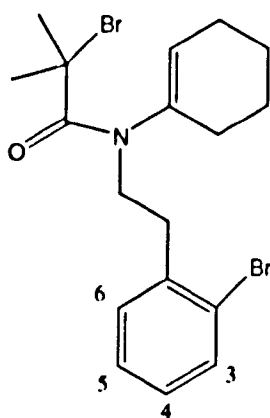


(2-Bromo-benzyl)-cyclohexylidene-amine (**190**) (2.0g, 7.5 mmol) and 2-bromo-2-methylpropionyl bromide (1.1 ml, 9.02 mmol) were reacted as described above (6.5.4). Purification by flash column chromatography eluting with 16:1 hexane:ethyl acetate

furnished 2-bromo-*N*-(2-bromo-benzyl)-*N*-cyclohex-1-enyl-2-methyl-propionamide (**191**) (0.6 g, 19%) as a yellow oil.

$\nu_{\max}$  (neat) /cm<sup>-1</sup> 2931, 2856, 1781, 1704, 1631, 1466, 1393, 1295, 1183, 1106, 1029;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.42-1.64 (6H, m, *CH*<sub>2</sub>), 1.99 (6H, s, C(Br)*CH*<sub>2</sub>*CH*<sub>3</sub>), 2.14-2.31 (2H, m, *CH*<sub>2</sub>), 4.11 (1H, br d, *J* 18.0, NCHH), 5.23 (1H, br d, *J* 18.0, NCHH), 5.12 (1H, t, *J* 3.5, NC=CH), 7.02 (1H, dt, *J* 8.0, *J* 1.5, H-4), 7.19 (1H, app dt, *J* 8.0, *J* 1.5, H-5), 7.43 (1H, app dd, *J* 8.0, *J* 1.5, H-6), 7.46 (1H, app dd, *J* 8.0, *J* 1.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 19.98 (t), 22.52 (t), 23.96 (t), 27.40 (t), 31.44 (2 x q), 51.07 (t), 57.68 (s), 121.21 (s), 128.83 (d), 126.47 (d), 127.57 (d), 128.20 (d), 131.41 (d), 135.74 (s), 136.82 (s), 169.46 (s); *m/z* (EI) 418 [(MH-<sup>81</sup>Br <sup>81</sup>Br)<sup>+</sup>, 25%], 416 [(MH-<sup>81</sup>Br <sup>79</sup>Br)<sup>+</sup>, 100%], 414 [(MH-<sup>79</sup>Br <sup>79</sup>Br)<sup>+</sup>, 61%], 336 (8), 291 (5), 170 (4).

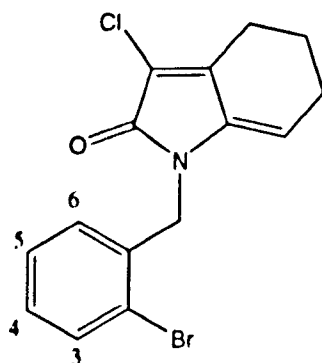
#### 6.5.4.3 2-Bromo-*N*-[2-(2-bromo-phenyl)-ethyl]-*N*-cyclohex-1-enyl-2-methyl-propionamide (**203**)



[2-(2-Bromo-phenyl)-ethyl]-cyclohexylidene-amine (**202**) (~2.0g, 10.0 mmol) and 2-bromo-2-methylpropionyl bromide (1.36 ml, 11.0 mmol) were reacted as described above (6.5.4). Purification by flash column chromatography eluting with 4:1 heptane:ethyl acetate furnished 2-bromo-N-[2-(2-bromo-phenyl)-ethyl]-N-cyclohex-1-enyl-2-methylpropionamide (**203**) (0.89 g, 22%) as a yellow oil.

$\nu_{\max}$  (neat) / $\text{cm}^{-1}$  2938, 1743, 1634, 1471, 1393, 1366, 1287, 1161, 1110, 1017;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.48-1.59 (4H, m,  $\text{CH}_2$ ), 1.62-1.70 (2H, m,  $\text{CH}_2$ ), 1.93 (6H, s,  $\text{C}(\text{Br})\text{CH}_2\text{CH}_3$ ), 2.04-2.09 (2H, m,  $\text{CH}_2$ ), 2.98 (2H, t,  $J$  8.0,  $\text{NCH}_2\text{CH}_2$ ), 3.24 (1H, br s,  $\text{NCHHCH}_2$ ), 3.70 (1H, br s,  $\text{NCHHCH}_2$ ), 5.69 (1H, br,  $\text{C}=\text{CHCH}_2$ ), 7.00 (1H, dt,  $J$  7.5,  $J$  1.5, H-4), 7.16 (1H, dt,  $J$  7.5,  $J$  1.5, H-5), 7.23 (1H, dd,  $J$  7.5,  $J$  1.5, H-6), 7.34 (1H, dd,  $J$  7.5,  $J$  1.5, H-3);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ) 21.09 (t), 22.43 (2 x t), 24.48 (t), 26.80 (t), 27.53 (2 x q), 48.52 (t), 58.05 (s), 124.32 (s), 127.41 (d), 127.92 (d), 128.20 (d), 130.95 (d), 132.76 (d), 137.88 (s), 138.18 (s), 163.86 (s);  $m/z$  (EI) 432 [ $(\text{MH}^{81}\text{Br}^{81}\text{Br})^+$ , 61%], 430 [ $(\text{MH}^{81}\text{Br}^{79}\text{Br})^+$ , 100%], 428 [ $(\text{MH}^{79}\text{Br}^{79}\text{Br})^+$ , 66%], 350 (42), 270 (3), 196 (4).

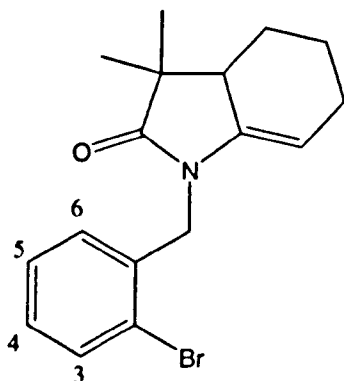
#### 6.5.5 1-(2-Bromo-benzyl)-3-chloro-1,4,5,6-tetrahydro-indol-2-one (205)



To a mixture of *N*-(2-bromo-benzyl)-2,2,2-trichloro-*N*-cyclohex-1-enyl-acetamide (**192**) (0.1 g, 0.24 mmol) and copper (I) chloride (24.0 mg, 0.24 mmol) under a nitrogen atmosphere was added a solution of tris-(2-pyridyl-methyl)-amine (**132**) (7.0 mg, 0.24 mmol) in dry dichloroethane (3.2 ml, 0.12M solution). The resulting mixture was stirred under reflux at 80°C for 48 hours. The mixture was then eluted through a silica plug with dichloromethane and subsequent removal of solvent under reduced pressure furnished 1-(2-bromo-benzyl)-3-chloro-1,4,5,6-tetrahydro-indol-2-one (**205**) (51.0 mg, 62 %) as a pale yellow oil.

$\nu_{\max}$  (neat) /cm<sup>-1</sup> 2932, 1717, 1657, 1558, 1433, 1340, 1318, 1144, 1027, 958;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.77 (2H, qn, *J* 6.0, CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.23 (2H, q, *J* 6.0, CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.58 (2H, t, *J* 6.5, CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 4.83 (2H, s, NCH<sub>2</sub>), 5.50 (1H, t, *J* 5.0, C=CHCH<sub>2</sub>), 6.92 (1H, d, *J* 7.5, H-6), 7.05 (1H, t, *J* 7.5, H-4), 7.16 (1H, t, *J* 7.5, H-5), 7.47 (1H, d, *J* 7.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 22.05 (t), 22.36 (t), 24.06 (t), 43.13 (t), 111.87 (d), 124.84 (s), 127.55 (d), 127.81 (d), 128.64 (d), 132.49 (d), 137.54 (s), 138.26 (s), 139.95 (s), 142.20 (s), 163.59 (s); *m/z* (EI) 340 [(MH-<sup>81</sup>Br)<sup>+</sup>, 100%], 338 [(MH-<sup>79</sup>Br)<sup>+</sup>, 74%], 306 (8), 260 (8), 226 (4).

## 6.5.6 1-(2-Bromo-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (204)

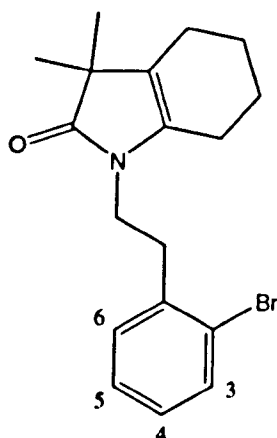


To a mixture of 2-bromo-*N*-(2-bromo-benzyl)-*N*-cyclohex-1-enyl-2-methylpropionamide (**191**) (0.2 g, 0.48 mmol) and copper (I) bromide (20.0 mg, 0.14 mmol) under a nitrogen atmosphere was added a solution of tris-(2-pyridyl-methyl)-amine (**132**) (42.0 mg, 0.14 mmol) in dry dichloromethane (0.12M solution). The resulting mixture was stirred at room temperature for 15 minutes. The mixture was then eluted through a silica plug with dichloromethane and subsequent removal of solvent under reduced pressure afforded 1-(2-bromo-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (**204**) (0.18 g, 90%) as a pale yellow oil.

$\nu_{\text{max}}$  (neat) /cm<sup>-1</sup> 2934, 1715, 1677, 1570, 1441, 1407, 1338, 1171, 1028;  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>) 1.09 (6H, m, CCH<sub>3</sub>CH<sub>3</sub>), 1.41-2.00 (6H, m, CH<sub>2</sub>), 4.42 (1H, d, *J* 16.0, NCHH), 4.73 (1H, t, *J* 3.5, CHC=CH), 4.93 (1H, d, *J* 16.0, NCHH), 5.24 (1H, br s, C=CH), 7.01 (1H, app t, *J* 7.5, H-4), 7.13-7.20 (2H, m, H-5, H-6), 7.47 (1H, d, *J* 7.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz, CDCl<sub>3</sub>) 20.06 (q), 23.32 (t), 24.81 (t), 24.90 (q), 25.94 (t), 44.32 (t), 49.16 (s), 100.84 (d), 123.07 (s), 125.17 (d), 127.89 (d), 128.09 (d), 128.54 (d), 133.14 (d), 136.07

(s), 143.66 (s), 180.35 (s);  $m/z$  (EI) 336 [(MH- $^{81}\text{Br}$ ) $^+$ , 15%], 334 [(MH- $^{79}\text{Br}$ ) $^+$ , 32%], 291 (60), 279 (27), 254 (3), 108 (8).

**6.5.7 1-[2-(2-Bromo-phenyl)-ethyl]-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (211)**



To a mixture of 2-bromo-*N*-[2-(2-bromo-phenyl)-ethyl]-*N*-cyclohex-1-enyl-2-methyl-propionamide (**203**) (0.1 g, 0.23 mmol) and copper (I) bromide (10.0 mg, 0.07 mmol) under a nitrogen atmosphere was added a solution of tris-(2-pyridyl-methyl)-amine (**132**) (20.0 mg, 0.07 mmol) in dry dichloromethane (0.12M solution). The resulting mixture was stirred at room temperature for 5 minutes. The mixture was then eluted through a silica plug with dichloromethane and the solvent removed under reduced pressure. Purification by flash column chromatography eluting with 20:1 heptane:ethyl acetate afforded 1-[2-(2-bromo-phenyl)-ethyl]-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (**211**) (30.0 mg, 8%) as a yellow oil.

$\nu_{\text{max}}$  (neat) / $\text{cm}^{-1}$  2936, 1707, 1676, 1568, 1472, 1394, 1355, 1116, 1016;  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ) 1.02 (6H, s,  $\text{CCH}_3\text{CH}_3$ ), 1.51-1.59 (4H, m,  $\text{CH}_2$ ), 1.82-1.89 (4H, m,  $\text{CH}_2$ ), 2.97

(2H, t,  $J$  7.0,  $\text{NCH}_2\text{CH}_2$ ), 3.57 (2H, t,  $J$  7.0,  $\text{NCH}_2\text{CH}_2$ ), 7.00 (1H, app dt,  $J$  7.5,  $J$  1.0, H-4), 7.09-7.18 (2H, m, H-5, H-6), 7.49 (1H, d,  $J$  7.5, H-3);  $\delta_{\text{C}}$ (75.5 MHz,  $\text{CDCl}_3$ ) 21.02 (t), 21.88 (t), 22.26 (t), 22.33 (2 x q), 23.39 (t), 33.06 (t), 40.13 (t), 46.12 (s), 127.89 (2 x d), 129.29 (2 x d), 133.13 (s), 137.04 (s), 138.78 (s), 139.97 (s), 178.15 (s);  $m/z$  (EI) 350  $[(\text{MH}^{81}\text{Br})^+, 80\%]$ , 348  $[(\text{MH}^{79}\text{Br})^+, 100\%]$ , 268 (4), 178 (6).



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